AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Claritin® Tablets and Syrup

(10 mg loratadine)

OTC Indication for Chronic Idiopathic Urticaria

BRIEFING BOOK

MARCH 2002

TABLE OF CONTENTS

Page(s)

INTRODUCTION

Schering Corporation (Schering) has submitted supplemental new drug applications (sNDAs) for Claritin® tablets and syrup (10 mg loratadine per dose) for over-the-counter (OTC) labeling for the indications of allergic rhinitis and chronic idiopathic urticaria (CIU), labeled as chronic or recurring hives of an unknown source. FDA has called this Advisory Committee meeting to discuss the merits of OTC labeling of loratadine for the treatment of recurring episodes of CIU. This briefing document addresses the following issues:

1. CIU is not associated or confused with more serious conditions.
2. CIU is currently managed by consumers as a self-treated condition.
3. Claritin is a very safe therapy in the treatment of CIU.
4. Physicians are comfortable with consumers' ability to self-recognize recurring episodes of CIU.
5. Adequate and understandable labeling can be developed for appropriate self-selection and safe and effective use of Claritin for CIU in an OTC setting.

Schering has conducted three new studies that support the above points:

- A physician practices study conducted among 359 physicians, designed to better understand their practices and opinions with respect to CIU.
- A consumer habits and practices study of 388 subjects diagnosed as having CIU, designed to better understand how they currently manage and treat CIU.
- A consumer self-recognition study of 196 CIU sufferers conducted in conjunction with a label comprehension study and designed to determine how well patients can accurately self-recognize (dermatologist confirmed) the conditions and symptoms of CIU.

BACKGROUND

A joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pulmonary and Allergy Advisory Committee was held on May 11, 2001, to consider the safety of loratadine (10 mg) for OTC use for allergic rhinitis. The Advisory Committees concluded that loratadine, 10 mg daily, is safe for OTC use for allergic rhinitis. Subsequent to this Advisory Committee meeting, Schering submitted sNDAs to FDA in support of the switch of Claritin to OTC status, not only for allergic rhinitis, but for CIU as well. Since the switch of Claritin for allergic rhinitis was previously considered by this committee, the April 22, 2002 NDAC meeting will focus on the additional OTC indication of CIU.

As Claritin, in 10 mg daily doses, is approved as a prescription drug for treating CIU for patients aged 6 years old and above, efficacy information is not included in this summary document. In addition, as this committee has already reviewed the efficacy and safety of loratadine for OTC marketing for allergic rhinitis, information on these topics is not provided. This briefing document does provide an abbreviated summary of the worldwide safety of loratadine for CIU and substantiation for the appropriateness of this indication for OTC labeling for consumers.

It should be noted that while Schering raised concerns regarding the third-party petition to switch second-generation antihistamines from prescription to OTC status for allergic rhinitis at the referenced May 11, 2001 joint Advisory Committee meeting, a number of factors have led Schering to now request the switch of Claritin to non-prescription status. At the previous joint Advisory Committees meeting, Schering expressed concerns that for many patients allergies are frequently chronic, complex diseases with serious co-morbidities requiring physician care. The vote of the Advisory Committees as well as FDA's strong support of a switch of loratadine, has led us to re-examine our position. We continue to believe that allergies often require physician oversight and management, particularly for patients with more chronic

conditions and related illnesses such as asthma. Our position has not changed in this regard. Nonetheless, with the continued availability of other prescription antihistamines for those patients requiring physician oversight, Schering believes the needs of both physicians and their patients can continue to be met, and that the issues previously raised should not preclude a switch of Claritin to OTC status, with appropriate labeling and an accompanying educational campaign.

CHRONIC IDIOPATHIC URTICARIA

CIU is a medical condition that is generally not associated or confused with *more serious conditions.*

Chronic idiopathic urticaria is defined as the persistence of urticarial lesions beyond 6 weeks duration for which an exogenous cause is not discovered despite an appropriate medical work-up to do so.[1] Urticarial lesions are generally easy to recognize since they typically occur in visible locations (e.g., face neck and extremities) and are associated with intense itching. Individual urticarial lesions typically fade within a 24-hour period and reappear elsewhere until the attack is resolved. Symptoms may be continuous, daily, weekly, or less frequent.[2] Symptoms range in severity from mild, which are responsive to antihistamines, to rarer, more severe exacerbations, which may not be amenable to treatment with antihistamines or, oftentimes with other prescribed medications. Sufferers of CIU often describe their affliction as severely intense itching that “keeps me awake all night”. In a recent study of 388 subjects with CIU conducted on behalf of Schering, most suffered, on average, 3 episodes per year, although 17% reported constant episodes. **(Appendix 1)**

Chronic idiopathic urticaria is a self-limited condition for most patients. Generally, 50% of patients undergo spontaneous remissions within 1 year, although approximately 20% continue to have symptoms intermittently for years. In a

prospective study of 220 adult patients with chronic urticaria who were followed for 1 to 3 years, 35% were symptom-free after one year and 25% underwent spontaneous remission after 1 year. At the end of the follow-up period, symptoms had improved in 98% of patients who still had symptoms.[3]

CIU patients are generally in good health. Rarely is food or dye allergy causally related to chronic urticaria and atopy is not a risk factor.[4] Systemic connective tissue disease or urticarial vasculitis is associated with less than 1 to 2% of chronic urticaria cases. In these rare patients, the presence of an immune disorder is usually evident because the individual urticarial lesions are atypical (they last longer than 24 hours, may be associated with prolonged skin discoloration or purpura, and may burn and hurt rather than itch), and may be associated with constitutional symptoms and laboratory abnormalities.[2] An epidemiological study based on the Swedish Cancer Registry of patients with chronic urticaria showed no association with malignancy.[4]

Chronic idiopathic urticaria cases are sometimes accompanied by angioedema (deep dermal, subcutaneous or submucosal edema),[5] which may affect the face, lips, tongue, or limbs.[1] Although the angioedema of CIU may be painful, it is not life-threatening, because, in contrast to hereditary angioedema, the angioedema of CIU is rarely associated with laryngeal edema.[6]

The symptoms of CIU are unlikely to be confused with the symptoms of an acute anaphylactic reaction.

In commenting on the treatment of “allergic itching related to hives and rashes” in the preamble to the 1992 Final Monograph for OTC Antihistamine Drug Products **(Appendix 2)**, FDA raised a theoretical concern that acute urticaria can be one component of a systemic anaphylactic reaction, and the use of an OTC antihistamine could delay more appropriate treatment.

We have found that this theoretical concern is unfounded. Firstly, anaphylactic reactions are not associated with CIU. Based on expert review, chronic idiopathic urticaria is neither considered a premonitory manifestation of anaphylaxis nor a risk factor for the development of anaphylaxis. Moreover, consumers understand the need for emergency medical care in the event of signs of anaphylaxis and are not likely to delay proper treatment. In a survey of 388 patients with CIU, ninety-five percent (95%) reported that they knew to seek immediate medical attention for symptoms of anaphylaxis (e.g., difficulty breathing, dizziness, trouble swallowing, feeling faint or other systemic reactions). **(Appendix 1)** Because anaphylactic reactions generally progress rapidly, it is unlikely that self-treatment under these conditions will occur or delay appropriate treatment.

In Canada and the UK, where loratadine has been OTC for more than 10 years, there have been no spontaneous case reports of anaphylaxis in treatment of chronic urticaria and only one case report in acute urticaria. This was the only case report in over an estimated 38 million courses of treatment with loratadine. The rarity of this occurrence is likely due to the high recognition and knowledge of proper treatment of anaphylactic reactions.

CURRENT CONSUMER AND PHYSICIAN PRACTICES IN CIU

CIU lesions are easy to recognize and second-generation antihistamines are first-line therapy for CIU.

Urticarial lesions are generally easy to recognize since they typically occur in visible locations and are associated with intense itching. Two recent studies conducted by Schering demonstrated that most patients **(Appendix 1)** (94%) and physicians **(Appendix 3)** (96%) find recurrent episodes of CIU easy for patients to recognize.

Treatment guidelines recommend "second-generation" antihistamines for first-line therapy since they are non-sedating when used at the recommended dosage.[9] Number or duration of wheals, or pruritis are reduced in 75% of CIU patients in response to antihistamine therapy. General management measures also include avoidance of triggers (e.g., alcohol overuse, overheating, aspirin, stress, etc.).[1]

Some physicians consider chronic idiopathic urticaria a "patient-diagnosed, physician-confirmed" condition. CIU appears to be self managed in most instances, as many physicians who treat CIU patients recommend that their patients keep prescribed and/or OTC antihistamines on hand in anticipation of the need to treat recurrent episodes. **(Appendix 3)** Since the lesions and pruritic symptoms are extremely irritating and bothersome, patients are compelled to contact their physicians for management when symptom severity increases, or the condition no longer responds to the self-selected antihistamine treatment.

Consumers in the U.S. already self-treat with OTC antihistamines.

As will be more fully described later in this paper, in many countries, newer non-sedating OTC antihistamines are already labeled to treat chronic idiopathic urticaria

and other allergic hive conditions. While OTC antihistamines in the United States are not currently labeled to treat the symptoms of CIU, they are nonetheless often used by the OTC consumer for this off-label condition. In a study of 388 subjects who have been diagnosed by a physician as having CIU, the key finding was that, in actuality, CIU is already a self-treated OTC condition in the United States. Almost two-thirds of CIU sufferers reported having used OTC antihistamine products to treat their hives prior to consulting a physician for diagnosis. Additional significant findings from this study included the following:

- CIU is a bothersome condition with nearly seven in ten sufferers rating it extremely or very bothersome. Continued itching/discomfort, hives that would not go away and the desire to find a cause of the hives were all key motivators for the initial physician visit.

- One third of sufferers claim to have not seen a physician in the past year for their chronic hives and nearly 20% of study subjects have not seen a physician since initial diagnosis. The behavior of not contacting the physician at every outbreak appears to be due, in part, to the use of over-the-counter medications and prescribed medications already on hand.

- CIU sufferers who do contact their physician when their hives recur appear to do so principally when symptoms do not respond to current treatment/medication or when more serious symptoms occur. These patients do not wait long before contacting their physician with over half making contact within one day.

- There is significant consistency in the symptoms described by CIU sufferers with nine in ten naming itching as the dominant symptom. Hives, wheals, redness and rash also receive high levels of mentions as key symptoms. The reported incidence of symptoms that could connote or be confused with anaphylaxis or angioedema is extremely low (swelling = 4%; breathing problems = 1%).

- When respondents were asked about what actions they would take if they experienced symptoms associated with anaphylaxis along with their hives (i.e., difficulty breathing or trouble swallowing), 95% of subjects indicated they would seek emergency care or call/visit their physician.

- Once diagnosed by a physician as having chronic idiopathic urticaria, 80% of study subjects perceive that it is "very easy" to identify the condition when it reappears. A total of 94% of subjects indicated that it was either "very" or "somewhat easy."

- Just under one quarter of study subjects indicate that the physician who diagnosed them with CIU recommended an over-the-counter medication, despite lack of indication approval and appropriate labeling guidelines and precautions. Benadryl® (diphenhydramine) was the most frequently mentioned OTC product. (Oral formulations of Benadryl are not indicated for any skin allergies and topical forms have limited indications for itching associated with rashes due to poison oak, ivy and sumac and insect bites and minor skin irritations).

In summary, this study has demonstrated that CIU is already a self-treated condition with OTC antihistamines playing an important role despite the lack of labeling for this condition. Sufferers of CIU are able to recognize recurrent episodes of the condition because of a number of important characteristics. Symptoms of CIU appear to be consistent and discrete. Changes in symptoms or the addition of other more troubling symptoms send signals to the consumer to seek immediate medical attention/physician contact. The frequency of occurrence for most diagnosed suffers provides an experience base with the condition that leads them to understand the natural patterns of the ailment. An outline of the consumer study protocol and summary of findings can be found in **Appendix 1**.

LORATADINE THERAPY FOR CIU

Claritin® is a very safe therapy in the treatment of CIU.

Loratadine is the world's leading non-sedating antihistamine. Loratadine tablets were first introduced in Belgium in February 1988, and later introduced in the United States in 1993 under the brand name of Claritin.

Loratadine is a very safe therapy, with low toxicity, an absence of significant risks from drug interactions, and a side effect profile similar to placebo. Additionally, loratadine has not been associated with drug abuse, and reports of misuse and drug overdose are rare. In the case of overdose, there have been no reports of serious adverse events indicating that a wide margin of safety exists at higher than recommended doses.

Loratadine is currently marketed in over 100 countries and is sold without a prescription in 28 countries. In 27 of these 28 countries, it is indicated for the treatment of skin allergies and/or chronic idiopathic urticaria. While these products are sold under pharmacist supervision in most of these countries (e.g., the United Kingdom, where it is now recommended for "General Sale" status), there is experience with unrestricted sale in other countries including Canada. This demonstrates that the medical community and consumers are comfortable with the self-treatment of chronic idiopathic urticaria.

A review of the post-marketing safety information in Canada and the UK, where loratadine has been sold over-the-counter for many years, demonstrated that there is a comparable safety profile between the loratadine non-prescription and prescription settings. Examples of the OTC labeling from Canada and the United Kingdom are attached. **(Appendix 4)**

Globally, loratadine is indicated for the treatment of allergic rhinitis and CIU at a dose of 10 mg once daily in adults and children 6 years of age and older. In September 2000, FDA approved Claritin Syrup for use in children down to 2 years of age, with a dose of 5 mg once daily for ages 2 years to less than 6 years. In the 14 years of marketing experience, with an estimated exposure of more than 13.7 billion patient days representing approximately 457 million courses of treatment, Claritin has demonstrated an exceptional safety profile. This safety experience was previously reviewed and accepted by the FDA and the Advisory Committees on May

11, 2001 as supporting the OTC use of loratadine. Accordingly, the experience is not detailed further here. FDA's summary of safety from the May 11, 2001 meeting can be found in **Appendix 5**.

In the US, the postmarketing safety surveillance (PMSS) database for Claritin from CIU patients was reviewed for potential safety signals. Overall, the types of spontaneous adverse events were consistent with the types recorded in the controlled clinical studies for CIU. No new safety signals were identified.

LABELING FOR CLARITIN® OTC

In determining the appropriate labeling for Claritin in the OTC treatment of CIU, Schering relied on data from the previously described consumer practices study (**Appendix 1**) along with data generated from a physician practices study (**Appendix 3**) and a self-recognition and label comprehension study (**Appendix 6**).

Physician research indicates CIU is easily recognizable and self-managed for patients previously diagnosed by a physician.

The Schering-sponsored physician practices study was conducted among 359 physicians (including primary care physicians, dermatologists, allergists and pediatricians) to better understand their practices and opinions regarding the diagnosis and self treatment of CIU. **(Appendix 3)** In this research, physicians who treat patients with chronic idiopathic urticaria reported a high level of confidence (96%) that a previously diagnosed patient is able to self-identify recurring episodes of CIU. **(Appendix 3)**

This research also demonstrates physicians feel that recurrent episodes of this condition are self-treatable by those patients who have been previously diagnosed with CIU. Once diagnosed, there is a high level of patient independence surrounding treatment of recurrent cases of chronic idiopathic urticaria. A majority of physicians interviewed instructed their CIU patients to keep prescription or over-the-counter (OTC) medication on hand in anticipation of treating a recurrent episode. When previously diagnosed patients contact their physician by phone for consultation regarding a CIU episode, 82% of physicians prescribe or phone-in prescriptions for treatment without a further patient visit. **(Appendix 3)**

Of the patients participating in a self-recognition study, almost all accurately self-recognized the condition and symptoms of CIU.

Based on the consumer and physician findings, Schering also conducted a self-recognition study in conjunction with a label comprehension study to confirm that consumers can accurately recognize recurrent symptoms after an initial physician diagnosis of CIU. **(Appendix 6)** In this study, subjects with a confirmed previous physician diagnosis of CIU were asked to either self-recognize an active recurrent episode of CIU or differentially identify an episode based on actual photographs and medical history. A dermatologist then consulted with the subject to confirm the accuracy of the subject's self-recognition. Of the 196 CIU sufferers who participated in the self-recognition study, almost all (94%) accurately self-recognized the condition and symptoms of CIU. An outline of the protocol for this study can be found in **Appendix 6**.

Adequate and understandable labeling can be developed for the safe and effective use of Claritin for CIU in an OTC setting.

The study data summarized above, along with the recommendations of experts in the fields of Dermatology and Allergy, led Schering to conclude that the OTC indication for Claritin should be for the treatment of recurring episodes of CIU following an initial physician diagnosis. While this position may be conservative, Schering believes it is appropriate.

There is precedent for initial physician diagnosis prior to self-treatment of recurring conditions in an OTC setting. The most recent, closely-related example of OTC drugs that are labeled for use following an initial physician diagnosis is analgesics for the relief of pain of migraine headaches. The labeling of these products, which were switched for this indication in 1997, states:

Ask a doctor before use if you have never had migraines diagnosed by a health professional.

Other clearly worded statements in the labeling of these products prompt the consumer to avoid inappropriate use and to seek medical care under conditions of increased risk.

A second earlier example occurred in 1990 when vaginal antifungals were switched from prescription to OTC status with labeling for use only by women who had previously experienced vulvovaginal candidiasis that has been diagnosed by a physician. Specifically, labeling for these products states:

If this is the <u>first</u> time you have had vaginal or vulvar itch and discomfort, consult your doctor. If you have had a doctor diagnose a vaginal yeast infection before and have the same symptoms now, use this cream as directed.

While these products have undoubtedly been used by some women who have not previously sought physician care, the extensive in-use experience over the past decade supports that most consumers can self-recognize based on signs and symptoms and will seek medical care if relief of symptoms is not realized in accordance with label instructions. Even those who have not been previously diagnosed appear to quickly seek medical care if symptoms are not relieved. Overall, the risk/benefit relationship and promptness of treatment through ready OTC access and rapid symptom relief has served the consumer well in this therapeutic category.

The successful safety records of these two categories of products over many years of use demonstrate that self-recognition, with a prior physician diagnosis, is a viable OTC option for conditions in which symptoms are reasonably obvious and recurrent.

Key Labeling for CIU

The key features of the proposed label for Claritin OTC for chronic idiopathic urticaria (labeled as "recurring or chronic hives of an unknown source") include the following:

Uses:

- **Relieves and reduces itching and rash due to recurring or chronic hives of an unknown source.**
- **Use only after being told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria).**

Warnings:

Seek Emergency Medical Attention if you have any of the following symptoms along with a rash, hives or an insect bite or sting:

- **Trouble swallowing**
- **Fever above 100°F**
- **Wheezing or problems breathing**
- **Hives or swelling in or around mouth**
- **Drooling**
- **Trouble speaking**
- **Joint pain**

Do not use unless you have been told by a doctor that you have recurring or chronic hives of an unknown source (chronic idiopathic urticaria.)

Do not use to treat food or drug allergies or insect bites or stings.

Ask a doctor if your itching or rash due to chronic or recurring hives does not improve after 5 days of treatment.

The proposed label has been tested among separate cohorts representing CIU sufferers, the general population, special populations for whom there are contraindications, acute hive sufferers, and individuals of lower literacy levels.[10] Results of this testing overall demonstrate that consumers understood the uses of Claritin, the label warnings, and directions with the exception of the findings noted below.

- When presented with correct and incorrect use scenarios, non-CIU sufferers demonstrated a strong understanding (66% - 97%). However, this level decreased (38% - 58%) when subjects were asked about the uses of the product on an "open-ended" basis. The most common incorrect answer given by acute hives sufferers (mentioned by 22% of subjects) was use of the product for "hives/itching due to hives." A conservative approach was taken in the data analysis and these responses were considered as incorrect. In fact, the answers are not entirely incorrect, since the responses encompass use of the product for recurring hives of an unknown source (CIU).
- When presented with a prototypical scenario of acute hives, three-fourths (75%) of acute hive sufferers understood Claritin is not indicated for this condition. When acute hive sufferers were asked whether Claritin is intended for their use, more than half (54%) either correctly de-selected the product or indicated they would ask their doctor prior to use.

Finally while the label tested did not indicate the product for use in treating "allergic rhinitis," subject familiarity with the Claritin Brand resulted in a relatively high percentage of subjects indicating this as an appropriate use. While, in fact, this is an accurate answer, the response was considered incorrect since it was not included in the label tested. It is likely that the brand recognition of Claritin influenced the responses.

It is clear from this testing that labeling can be developed that clearly conveys the directions for use and warnings to enable sufferers of chronic idiopathic urticaria to appropriately and safely use Claritin for self treatment. Further, the labeling can also be developed to encourage appropriate self selection for use. While minor revisions to the labeling can further enhance communication, this testing demonstrates that OTC labeling has been developed for safe use that is understood by consumers.

RISK/BENEFIT SUMMARY

A Risk/Benefit Analysis of the current state of treating CIU in the United States clearly supports the OTC use of Claritin for CIU.

As was clearly demonstrated in the consumer and physician studies, there is currently a high level of off-label use of OTC antihistamines in CIU. This usage is occurring without the consumer having access to any CIU labeling. Consequently, the OTC consumer currently treats CIU without any directions for use. While we did not find any evidence that this off-label use has resulted in a serious safety issue, the lack of labeled directions for use is clearly not in the best interests of public health.

As discussed above, second-generation, non-sedating antihistamines are currently first- line therapy in treating CIU. Loratadine is a very safe treatment for allergic conditions and CIU, based on its experience exceeding 13 billion patient days of exposure. As an OTC medication, Claritin will offer the benefits of treating CIU with a safe and effective therapy, along with proper labeling for appropriate self-management. Furthermore, along with consumer-friendly labeling, Schering is committed to support Claritin as an OTC medication with a comprehensive patient/consumer education campaign directed at the proper management of allergies and chronic idiopathic urticaria. The program will provide consumers with information on allergies and potential accompanying conditions as well as CIU, and recommendations for recognizing when there is a need for patients to remain in close communication with their treating physicians.

Concern has been raised that in an OTC setting, patients may self-treat acute urticaria (or hives) prior to identification of the causative agent. Based on research on CIU patients who widely use OTC antihistamines prior to physician diagnosis, it is likely that acute hive suffers are already using OTC antihistamines. Claritin, as an OTC medication with the proposed labeling and education campaign, will direct patients with acute urticaria to contact a physician.

Schering has recommended that the label for OTC Claritin direct a consumer to obtain an initial diagnosis for CIU prior to self-treating. The role of the physician in diagnosing and educating the consumer about CIU is beneficial to appropriate self care in affected patients. If the cause of the urticaria can be identified and avoided, better patient outcomes and a greater safety margin will result. Based on the recent physician and consumer CIU studies, as well as the self-recognition study, initial physician diagnosis facilitates accurate patient recognition of recurrent episodes which makes self treatment more appropriate.

While use of non-sedating antihistamines in acute hives is not inappropriate therapy, the need to identify and avoid the causative allergen is best managed by initial physician consultation. In the case that a patient fails to seek medical care for CIU, it is important to point out that in the vast majority of patients with hives, chronic idiopathic urticaria is not serious or life threatening, but rather is a bothersome condition that affects quality of life. In the small percentage of patients whose hives are associated with systemic illness (e.g., connective tissue disease), the concomitant symptoms of fever, fatigue, and weight loss, as well as product labeling, should prompt patients to seek a timely medical evaluation.

The switch of Claritin from prescription to OTC status in the United States should not result in any increased safety risk to patients with chronic idiopathic urticaria currently using prescription Claritin. Perhaps more importantly, for the OTC consumer currently using OTC antihistamines off-label to treat CIU, the availability of

Claritin with labeled instructions for proper treatment will clearly result in a positive shift in the risk-benefit profile of OTC treatments.

CONCLUSION

The safety and efficacy profile of loratadine, as well as the label comprehension study results, and the patient and physician studies, all strongly support OTC use of loratadine for the treatment of CIU.

Based on the consumer and physician studies reported here, it is clear that chronic idiopathic urticaria is currently a self-diagnosed and OTC-treated condition. Current behavior among consumers demonstrates that currently available OTC antihistamines are already widely used for this condition. Consumers often use over-the-counter antihistamines prior to seeking a diagnosis; and after diagnosis, many consumers use OTC medications on the recommendation of their physician. A sizeable proportion of sufferers have not seen a physician for CIU since initial diagnosis and therefore, self- managing the condition is common practice. Many physicians encourage self-management by prescribing medications with multiple refills in advance of outbreaks, which are easily recognized by patients and frequently do not require subsequent physician visits.

The excellent safety profile originally demonstrated for loratadine in the controlled clinical studies has been upheld in 14 years of post-marketing safety surveillance during which an estimated 457 million courses of treatment were sold. Based on the analyses of the post-marketing safety information in countries where OTC loratadine is already used to treat CIU, the established safety profile of loratadine should not change by OTC switch. Skin disorders responsive to antihistamines have been safely managed with OTC loratadine in several major markets, including the UK and Canada. Finally, it has been demonstrated that clear, comprehensible labeling can

be developed for safe and effective OTC use for chronic hives of an unknown source. With adequate labeling instructions, Claritin is appropriate for the self-treatment of CIU in an OTC setting.

Based on the outcome of the May 11, 2001 Joint Advisory Committees meeting, it is clear that FDA is predisposed to switching Claritin to OTC status for allergic rhinitis. As OTC antihistamines are currently used to self-treat chronic idiopathic urticaria, even without an initial physician diagnosis, it is in the best interest of the consumer to also switch the CIU indication, as proposed, for Claritin. This will give the consumer the best information available to self-manage CIU, and direct the consumer to the physician where self-treatment is not appropriate. In addition, there is a large population of CIU sufferers who currently treat with prescription Claritin. Brand recognition and easy access without a prescription will lead many of these patients to the OTC product, even if only labeled for allergic rhinitis. Providing CIU information on the OTC label is also in the best interest of these consumers.

In conclusion, Claritin is safe for the self-treatment of chronic idiopathic urticaria when labeled with appropriate directions for use.

REFERENCES

1. Sabroe RA and Greaves MW. Chronic idiopathic urticaria and its management. Dermatologic Therapy 2000;13:384-391.
2. Fox R.X. Chronic Urticaria: mechanisms and treatment. Allergy and Asthma Proc 2001:22(2):97-100.
3. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol 2001;45:387-391.
4. Lindelof B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. 1990; 123:453-456.
5. Greaves M. Current reviews of allergy and clinical immunology: chronic urticaria. J Allergy Clin Immunol 2000;105 (4):664-672.
6. Cooper KD. Urticaria and angioedema: diagnosis and evaluation. J Am Acad of Dermatol 1991;25 (1):166-176.
7. Wanderer AA, Bernstein IL, Goodman DI, et al. The diagnosis and management of urticaria: a practice parameter Part I: acute urticaria/angioedema Part II; chronic urticaria/angioedema. Ann Allergy Asthma Immunol 2000;85:521-544.

LIST OF APPENDICES

Dermatologic Therapy, Vol. 13, 2000, 384–391
Printed in the United States · All rights reserved

DERMATOLOGIC THERAPY
ISSN 1396-0296

Chronic idiopathic urticaria and its management

R.A. SABROE & M.W. GREAVES
St. John's Institute of Dermatology, Guy's, King's and St. Thomas's School of Medicine, King's College London, St. Thomas's Hospital, London

ABSTRACT: Chronic urticaria is defined as the daily or almost daily occurrence of wheals for at least 6 weeks. This disorder affects 0.1% of the general population and is more common in females. Recently a subgroup of patients with chronic urticaria has been found to have circulating autoantibodies directed against the high-affinity IgE receptor (FcεRI) or against IgE antibodies. These "autoantibodies" are felt to play a role in mast cell histamine release. Urticaria patients with these circulating antibodies also have a higher prevalence of other autoimmune diseases. The management of patients with chronic urticaria is to identify and eliminate the underlying cause, however, an etiology for chronic urticaria is rarely identified. Thus the approach to treatment usually centers on the use of antihistamines initially with the addition of other immune modulating agents as necessary.

KEYWORDS: chronic idiopathic urticaria, anti-IgE antibodies, anti-IgE receptor antibodies, antihistamines.

Chronic idiopathic urticaria

Urticaria consists of edematous, pink or red, usually itchy wheals, which fade over the course of 24 hours leaving no trace. It is thought that approximately 20% of the population has an episode of urticaria at some time in their lives (1).

We define chronic idiopathic urticaria (CIU) as the daily or almost daily occurrence of wheals for at least 6 weeks, where predominant physical urticarias and urticarial vasculitis (see below) have been excluded (2). CIU has a prevalence of at least 0.1% in the population and is more common in women (3,4). Approximately 40% of patients have associated delayed pressure urticaria, and 50% have angioedema (see below) (4–6). A cause for CIU is rarely identified. In a small number of cases, food additives such as benzoic acid compounds and azo dyes may exacerbate CIU. Drugs (such as antibiotics, particularly penicillin, aspirin and non-steroidal anti-inflammatory drugs, opiates, and angiotensin-converting enzyme inhibitors), alcohol, intercurrent febrile illnesses, and psychological stress may also worsen CIU (2,4,6). CIU may be a disabling condition, and patients with CIU have similar scores on the Nottingham health profile (a quality of life questionnaire) as patients with chronic ischemic heart disease (7). CIU has a chronic relapsing course in which 20% of patients still have active disease after 10 years (6).

Address correspondence and reprint requests to: Ruth A. Sabroe, MD. Professorial Unit, St. John's Institute of Dermatology, Guy's, King's and St. Thomas's School of Medicine, King's College London, St. Thomas's Hospital, London SE1 7EH, UK.

Other types of urticaria

Urticaria may be acute or chronic. Acute urticaria, in which symptoms persist for less than 6 weeks, is the most common type of urticaria. Unlike chronic urticaria, a cause can be identified in up to 50% of cases. Causes include type I hypersensitivity reactions to foods (e.g., fruits, seafood, nuts, dairy products), wasp and bee stings, blood products, radiocontrast media, viral infections, or febrile illnesses. Drugs, including those listed for chronic urticaria, and the ingestion of larvae of

fish nematodes, such as *Anisakis simplex*, may also cause acute urticaria (8,9).

Chronic urticaria may be physical or idiopathic. CIU is described above. In physical urticarias, wheals are reproducibly induced by a specific physical stimulus. They include those induced by sustained pressure against the skin (delayed pressure urticaria), stroking or rubbing (dermographism), sweating triggered by exercise, emotion, or heat (cholinergic urticaria), heat (localized heat urticaria), cold (cold urticaria), vibration (vibration urticaria), sunlight (solar urticaria), and water (aquagenic urticaria). Wheals characteristically occur within a few minutes of contact with the stimulus and fade within 2 hours. The exception is delayed pressure urticaria in which wheals appear 6–12 hours after the application of sustained pressure, and last for up to 3 days (10).

The wheals of urticarial vasculitis may be similar in appearance to those of CIU, but they tend to be of longer duration (more than 24 hours), may be painful or tender as well as itchy, and may leave residual purpura or pigmentation. Urticarial vasculitis is more likely than CIU to be associated with systemic symptoms such as arthralgia or fever, with systemic disease such as systemic lupus erythematosus, and to be resistant to treatment with antihistamines (2,11). The diagnosis of urticarial vasculitis is made from a biopsy specimen with characteristic histopathologic features consisting of venular endothelial cell swelling, extravasation of red cells, leukocytoclasis, and fibrin deposition. Structural vascular damage is absent in the wheals of other urticarias (12).

Angioedema is characterized by sudden, localized swellings of skin or mucous membranes that fade during the course of 24–48 hours. Histologically the edema involves both the dermis and subcutaneous tissues, distinguishing it from urticaria, which involves only the dermis. Sites which may be involved include the face, lips, tongue, hands and feet, genitalia, and gastrointestinal mucous membranes. Involvement of the respiratory tract may be fatal (13). Approximately 50% of patients with CIU also have angioedema (6,14).

Pathogenic mechanisms of wheal formation in CIU

The pathogenic mechanisms of wheal formation and itching are not fully understood and have been reviewed recently (15). However, the mast cell is thought to be the primary effector cell. Mast cell stimulation with release of inflammatory mediators (listed in Fig. 1) causes inflammation and the accumulation and activation of other cells, including eosinophils and neutrophils, with the release of further inflammatory mediators. The intradermal injection of histamine produces a wheal and flare response with itching, similar to an urticarial wheal. Indeed, increased levels of histamine have been found in urticarial wheals. However, since a histamine-induced wheal lasts for only 30 minutes, it is likely that other inflammatory mediators are involved in wheal formation in CIU (15).

The discovery of autoantibodies against the high-affinity IgE receptor (FcεRIα) and/or IgE in patients with CIU

Although degranulation and mediator release from mast cells are implicated in the pathogenesis of CIU, a specific antigenic stimulus can rarely be identified. However, the intradermal injection of autologous serum (autologous serum skin test) produces a wheal and flare response in a proportion of patients with CIU, implying involvement of circulating serum histamine releasing factors (16–18). We have shown that some of these patients have autoantibodies that release histamine from both basophils and mast cells in vitro. These autoantibodies are directed against the high-affinity IgE receptor (FcεRI) in 25–30% of all patients and against IgE in 5–7% of all patients with CIU (Fig. 1) (18–20). The presence of autoantibodies has been confirmed by other groups using basophil histamine release assays, Western blot analysis, and enzyme-linked immunosorbent assay (21–24). Overall, autoantibodies are thought to occur in 30–50% of patients with CIU.

The cause of mast cell degranulation in the remaining 50–70% of patients remains unclear. Some patients may have low levels of anti-FcεRIα and anti-IgE autoantibodies, undetectable by current methods, or levels which fluctuate depending on disease severity. In a small number of patients a mast cell-specific histamine releasing factor(s) has been identified, which releases histamine from mast cells but not from basophils. This factor is a heat stable, nonimmunoglobulin G mediator not inhibited by preincubation with soluble

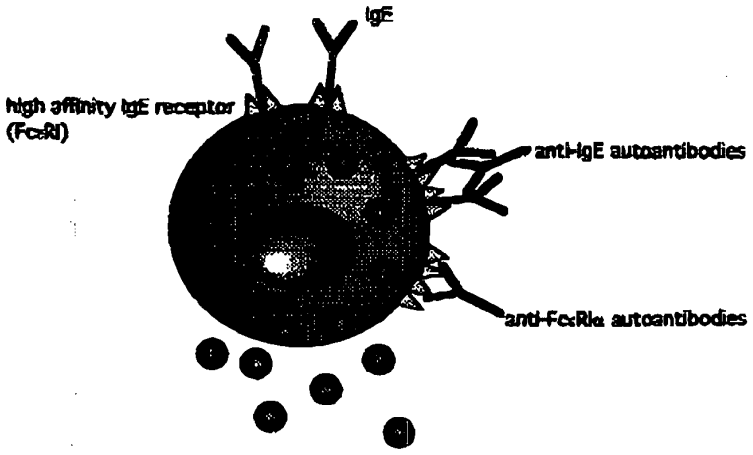


Fig. 1. Mast cell degranulation in CIU.

FcεRIα or IgE, but with a time course of action similar to that of stimulation of the mast cell via FcεRIα (17,18). This factor was originally thought to occur in up to one-third of patients, but we now believe that it is present in approximately 10% of patients with CIU (14).

Are anti-FcεRIα and anti-IgE autoantibodies specific to CIU?

Anti-FcεRIα autoantibodies have not been detected in serum from healthy control subjects, in patients with atopic dermatitis or psoriasis, or in patients with cholinergic urticaria or dermographism (25,26). However, anti-FcεRIα autoantibodies have been found in serum from patients with dermatomyositis, pemphigus vulgaris, bullous pemphigoid, and in systemic lupus erythematosus (26). Unlike the anti-FcεRIα autoantibodies found in CIU, these autoantibodies do not cause histamine release from basophils. In addition, they are predominantly of isotypes IgG 2 and 4, whereas in CIU anti-FcεRIα autoantibodies are largely of isotypes IgG 1 and 3 (26). Since complement fixation occurs predominantly with IgG isotypes 1 and 3, this raises the possibility of the involvement of complement in mast cell histamine release by autoantibodies in CIU (26,27).

Anti-IgE autoantibodies have been found in patients with atopic dermatitis and asthma, as well as in healthy subjects (21,28–30). However, unlike the anti-IgE autoantibodies found in CIU, there are very few reports of anti-IgE autoantibodies that can release histamine from basophils or mast cells in atopic patients, and their role in atopic disease is unclear. There are no published data on the IgG isotypes of anti-IgE autoantibodies in CIU.

Does the presence of anti-FcεRIα and anti-IgE autoantibodies effect the clinical or histopathologic features of CIU?

We compared the clinical and histopathologic features of patients with and without autoantibodies, as detected in basophil histamine release assays (14,31). There was considerable overlap between patients in the two groups, and it would not be possible to distinguish between them using clinical or histopathologic features alone. However, we found that patients with autoantibodies had more severe urticaria than patients without autoantibodies, particularly in the first 12 months of the disease. Patients with autoantibodies also had lower serum IgE levels than patients without autoantibodies, perhaps because the IgE–anti-IgE immune complex formation reduced the amount of detectable free IgE in patients with anti-IgE autoantibodies (14).

In support of an autoimmune basis for CIU in patients with anti-FcεRIα and/or anti-IgE autoantibodies, we found that other autoimmune diseases were more common in this group (14). Similarly, previous studies have shown clustering of antimicrosomal antibodies and abnormal thyroid function tests in patients with CIU with anti-FcεRIα and/or anti-IgE autoantibodies (32). Human leukocyte antigen (HLA) typing has also shown an in-

crease in HLA-DRB1*04 (DR4) and associated HLA-DQB1*0302 (DQ8) in patients with CIU with autoantibodies (33).

Histopathologically there was no difference between patients with and without autoantibodies in the number of neutrophils and T lymphocytes in uninvolved skin or infiltrating wheals of less than 4 or more than 12 hours duration. Patients without autoantibodies had more activated eosinophils in wheals of more than 12 hours duration than patients with autoantibodies (31). The significance of this finding is unclear, but it is consistent with the finding that wheals lasted for longer periods of time in patients without autoantibodies (14). Although the mast cell is thought to be the primary effector cell in CIU, basophils, which express FcεRIα, may also play a role. In patients with autoimmune CIU, there is a marked reduction in circulating basophil numbers. There is also a reduction in histamine release from patients' basophils to stimuli acting through FcεRI, indicating possible receptor desensitization (34). Basophils have been shown to accumulate in skin in the late-phase response (35,36), and it is possible that the same occurs in urticaria, where they may contribute to wheal formation by the release of inflammatory mediators including histamine.

Management

There are no published trials comparing the responses of patients with and without autoantibodies to the various treatment modalities available. Therefore, in most instances, patients with CIU are treated according to disease severity and therapeutic response, regardless of the presence or absence of autoantibodies. Exceptions, such as plasmapheresis, which we reserve for severely affected patients with autoimmune CIU, are discussed below. As in other forms of urticaria, there is no curative treatment for CIU, and management is aimed at the alleviation of symptoms.

Avoidance of exacerbating factors

Patients should be advised to avoid aspirin and other nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, opiates, and alcohol. Low-dose aspirin for cardiovascular disease is often tolerated, however, CIU is often exacerbated by warmth, and a cool ambient temperature may help, especially at night. In a small number of patients, avoidance of food additives may be beneficial.

Antihistamines

Antihistimines (Table 1) remain the first treatment option (37). Three-fourths of patients with CIU are likely to derive benefit, either in the control of itch or in the reduction in frequency, number, or duration of wheal (6). Nonsedating antihistamines are useful for daytime symptoms. In 80% of patients with CIU, itching is worse during the evening and at night (14), and sedating antihistamines may then be indicated. Initially a single morning dose of a nonsedating antihistamine should be given, for example, loratidine 10 mg or fexofenadine 180 mg. However, a combination of daytime nonsedating and nocturnal sedating antihistamines is often required to achieve 24-hour relief of symptoms. In this case, the best choice is usually hydroxyzine 25 mg administered in the evening in addition to a morning dose of one of the nonsedating antihistamines. In our experience, it may become necessary in severely affected patients to increase the dosage of the low-sedation antihistamines above the recommended levels. For example, loratidine 20 mg/day or fexofenadine 360 mg/day, although in these doses loratidine, but not usually fexofenadine, may cause noticeable sedation. Paradoxically any antihistamine can rarely cause an exacerbation of the urticaria.

Care should be taken with terfenadine, astemizole, and mizolastine, which can cause cardiac QT prolongation and tachyarrythmias. These drugs should not be used in combination with each other or with other drugs known to lengthen the QT interval, such as tricyclic antidepressants, antipsychotic drugs, sotolol, amiodarone, or quinidine, and dosages should not exceed those specified by the manufacturer. Terfenadine, astemizole, and mizolastine are metabolized by cytochrome P-450 and should not be used together or in combination with doxepin, macrolide antibiotics (e.g., erythromycin and clarithromycin), imidazole antifungal agents, cimetidine, or other P-450 inhibitors. Grapefruit juice inhibits terfenadine metabolism. Terfenadine is gradually being replaced by its active metabolite, fexofenadine, which is not metabolized by cytochrome P-450, and is also thought to carry a much lower risk of cardiotoxic effects (38).

The tricyclic antidepressant doxepin is a potent H_1 and H_2 receptor antagonist (39), and al-

Table 1. Antihistamines

Generic name	Proprietary name	Oral dose (adult)
Some sedating antihistamines		
Brompheniramine	Dimotane	8–24 mg twice a day slow release tablets or 4–8 mg three or four times a day
Chlorpheniramine	Piriton	4 mg every 4–6 hours (maximum 24 mg/day)
Clemastine	Tavegil	1 mg twice a day
Cyproheptadine	Periactin	4 mg three or four times a day
Diphenhydramine	Benadryl	25–50 mg every 4–6 hours (maximum 300 mg/day)
Hydroxyzine	Atarax	10–25 mg three times a day and 25–50 mg at night
Promethazine	Phenergan	10–25 mg two or three times a day
Trimeprazine	Vallergan	10 mg two or three times a day
Nonsedating antihistamines		
Acrivastine	Semprex	8 mg three times a day
Astemizole	Hismanal	10 mg once a day
Cetirizine	Zyrtec	10 mg once a day
Fexofenadine	Telfast	180 mg once a day
Loratidine	Clarityn	10 mg once a day
Mizolastine	Mizollen	10 mg once a day
Terfenadine	Triludan	60 mg twice a day or 120 mg once a day

though not licensed for use in urticaria, may be used instead of a sedating antihistamine at night. Patients show significant genetic polymorphism in the metabolic pathways for doxepin. Thus some patients tolerate large daily doses of 50 mg or even 100 mg, whereas others tolerate a maximum dose of only 10–20 mg. Doxepin should not be used with other drugs metabolized by or inhibiting cytochrome P-450, or which prolong the QT interval (including terfenadine, astemizole, and mizolastine), or with monoamine oxidase inhibitors. The addition of H_2 receptor antagonists may produce a small additional benefit in some patients, although the gain is often not clinically useful (40).

In pregnancy, while there is no conclusive evidence that antihistamines are teratogenic, no antihistamine can be considered safe. If an antihistamine is required, chlorpheniramine may be used in the first two trimesters, but should be avoided in the third trimester because of the risk of severe reactions in neonates, such as seizures. Antihistamines may appear in breast milk and may inhibit lactation, and therefore are not recommended.

Oral steroids

Systemic steroids should be avoided because tolerance develops, increasing dosages are needed to achieve control, and adverse effects are common. A short course of systemic steroids can occasionally be justified for severe exacerbations. If, for example, a patient with severe urticaria needs to be clear of symptoms for a specific social or occupational event, it is often reasonable to prescribe a short tapering course, beginning with prednisolone 40 mg/day for 5 days, reducing progressively to zero over the following 10 days.

Topical treatment

One percent menthol in aqueous cream may alleviate itch in some patients, and patients should be advised to apply this ad lib on an as-required basis (41). Topical steroids, antihistamines, and local anesthetics are not useful.

Leukotriene inhibitors

These drugs have recently been licensed for use in asthma (42). The authors have limited experience in the use of these drugs in CIU. The specific circumstances under which the prescription of leukotriene inhibitors should be contemplated have not been established. Although two small trials (published in abstract form) have shown encouraging results (43,44), there are also reports that these drugs may exacerbate aspirin-sensitive urticaria (45). It is prudent to await the results of adequately controlled studies in CIU before proposing guidelines for their use.

Other treatment strategies

For patients with severe disabling disease unresponsive to conventional treatment, improvement has

been achieved with cyclosporin A, intravenous immunoglobulins, and plasmapheresis (46–50). These treatments are not licensed in the United Kingdom for use in CIU.

There is evidence that the use of cyclosporin may be beneficial for patients with CIU, although it is probably suppressive rather than curative. In one study, 9 of 12 patients with CIU undifferentiated for the presence of autoantibodies responded to cyclosporin given for 4 weeks at a dose of 2.5–3.5 mg/kg (48). In another study, 13 of 19 patients given 1–3 mg/kg cyclosporin were in full remission after 3 months of treatment (49). In the second study, patients were investigated for the presence of histamine releasing factors using the autologous serum skin test, and results of this test did not correlate with response to treatment. However, in a more recent study, the effectiveness of cyclosporin in autoimmune CIU has been confirmed (50), and, in our experience, although such patients are generally more responsive than those without autoantibodies, the drug is usually effective in both categories, but a formal comparison has not yet been made. In practice, cyclosporin is reserved for severely incapacitated patients in whom inadequate control has been achieved with antihistamines. Cyclosporin is usually prescribed for a period of up to 3 months, although one of the authors (M.W.G.) has experience with its use continuously for much longer periods. The starting dose is 2.5–4 mg/kg/day, the aim being to achieve the lowest dosage compatible with 90% improvement in the patients symptoms. After up to 3 months of treatment the drug can be withdrawn without tapering, and in our experience there is no evidence of rebound. In one of the author's experience (M.W.G.), approximately one-third of patients remain in remission after treatment withdrawal, one-third relapse but are easily controlled by antihistamines, and one-third relapse to their former severity. In these patients a further course of cyclosporin needs to be considered. The recommended precautions must be taken before and during treatment, including the monitoring of renal function and blood pressure. A prior history of cancer or precancer (cervical dysplasia, etc.) would be a contraindication to treatment.

Intravenous immunoglobulins (IVIG) is an expensive treatment requiring an inpatient admission. We have shown that IVIG, using a total dose of 2 mg/kg over 5 days, produced improvement in 9 of 10 patients with positive autologous serum skin tests, 3 of whom were still in remission 3 years later (46). Like cyclosporin, although IVIG is effective in autoimmune CIU, one author (M.W.G.) found it to be effective, but less so in nonautoimmune CIU. However, there are no published data on the use of intravenous immunoglobulins in patients without autoantibodies. Treatment should be reserved for severely incapacitated patients with antihistamine-resistant disease. In general we use it rather rarely for patients who are intolerant of, unresponsive to, or for other reasons unsuitable for cyclosporin.

The above comments and indications for IVIG also apply to plasmapheresis. We published the treatment of eight patients with CIU with positive autologous serum skin tests with plasmapheresis, and six gained benefit for between 3 and 8 weeks (47). There are no published data on the use of plasmapheresis in patients without autoantibodies.

Summary

CIU has a prevalence of at least 0.1% in the population and is as disabling as ischemic heart disease in some patients. It is now established that 30–50% of patients with CIU have circulating functional autoantibodies against FcεRI and/or IgE. The cause of mast cell degranulation in the other 50–70% of patients is unclear at present. There is considerable overlap between the clinical and histopathologic features of patients with and without autoantibodies, but patients with autoantibodies have more severe urticaria than patients without autoantibodies, particularly in the first 12 months of disease. Patients with autoimmune CIU also have more associated autoimmune diseases and an increase in HLAs DR4 and DQ8. Treatment of severe CIU unresponsive to antihistamines may be difficult. However, there is some evidence to support the use of cyclosporin in any patient with severe CIU, and intravenous immunoglobulins and plasmapheresis in patients with autoantibodies.

References

1. Sheldon JM, Mathews KP, Lovell RG. The vexing urticaria problem: present concepts of etiology and management. J Allergy 1954: 25: 525–560.
2. Greaves MW. Chronic urticaria. N Engl J Med 1995: 332: 1767–1772.
3. Hellgren L. The prevalence of urticaria in the total population. Acta Allerolog 1972: 27: 236–240.

4. Sibbald RG, Cheema AS, Lozinski A et al. Chronic urticaria: evaluation of the role of physical, immunologic, and other contributory factors. Int J Dermatol 1991: 30: 381–386.
5. Barlow RJ, Warburton F, Watson K et al. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol 1993: 29: 954–958.
6. Champion RH, Roberts SOB, Carpenter RG et al. Urticaria and angio-oedema: a review of 554 patients. Br J Dermatol 1969: 81: 588–597.
7. O'Donnell BF, Lawlor F, Simpson J et al. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997: 136: 197–201.
8. Zuberbier T, Iffländer J, Semmler C et al. Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Derm Venereol (Stockh) 1996: 76: 295–297.
9. Del Pozo MD, Audicana M, Diez JM et al. *Anisakis simplex*, a relevant etiologic factor in acute urticaria. Allergy 1997: 52: 576–579.
10. Jorizzo JL, Smith EB. The physical urticarias: an update and review. Arch Dermatol 1982: 118: 194–201.
11. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol 1992: 26: 441–448.
12. Monroe EW. Urticarial vasculitis: an updated review. J Am Acad Dermatol 1981: 5: 88–95.
13. Greaves M, Lawlor F. Angioedema: manifestations and management. J Am Acad Dermatol 1991: 25: 155–165.
14. Sabroe RA, Seed PT, Francis DM et al. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcεRI or anti-IgE autoantibodies. J Am Acad Dermatol 1999: 40: 443–450.
15. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1996: 23: 735–740.
16. Grattan CEH, Wallington TB, Warin RP et al. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. Br J Dermatol 1986: 114: 583–590.
17. Kermani F, Niimi N, Francis DM et al. Characterization of a novel mast cell-specific histamine releasing activity in chronic idiopathic urticaria (CIU) (abstract). J Invest Dermatol 1995: 105: 452.
18. Niimi N, Francis DM, Kermani F et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996: 106: 1001–1006.
19. Grattan CEH, Francis DM, Hide M et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 1991: 21: 695–704.
20. Hide M, Francis DM, Grattan CEH et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993: 328: 1599–1604.
21. Fiebiger E, Maurer D, Holub H et al. Serum IgG autoantibodies directed against the α chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995: 96: 2606–2612.
22. Tong LJ, Balakrishnan G, Kochan JP et al. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997: 99: 461–465.
23. Zweiman B, Valenzano M, Atkins PC et al. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996: 98: 89–98.
24. Ferrer M, Kinét J-P, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-FcεRIα (α-subunit) in chronic urticaria. J Allergy Clin Immunol 1998: 101: 672–676.
25. Sabroe RA, Grattan CEH, Francis DM et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999: 140: 446–452.
26. Fiebiger E, Hammerschmid F, Stingl G et al. Anti-FcεRIα autoantibodies in autoimmune-mediated disorders. Identification of a structure-function relationship. J Clin Invest 1998: 101: 243–251.
27. Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol 1999: 104: 169–172.
28. Marone G, Casolaro V, Paganelli R et al. IgG anti-IgE from atopic dermatitis induces mediator release from basophils and mast cells. J Invest Dermatol 1989: 93: 246–252.
29. Nawata Y, Kulke T, Hosokawa H et al. Anti-IgE autoantibody in patients with atopic dermatitis. J Immunol 1985: 135: 478–482.
30. Twena DM, Marshall JS, Haeney MR et al. A survey of nonatopic and atopic children and adults for the presence of anti-IgE autoantibodies. Clin Immunol Immunopathol 1989: 53: 40–51.
31. Sabroe RA, Poon E, Orchard GE et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. J Allergy Clin Immunol 1999: 103(3 pt 1): 484–493.
32. O'Donnell BF, Swana GT, Kobza Black A et al. Organ and non organ specific auto-immunity in chronic urticaria [abstract]. Br J Dermatol 1995: 133(suppl 45): 42.
33. O'Donnell BF, O'Neill CM, Francis DM et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br J Dermatol 1999: 140: 853–858.
34. Sabroe RA, Francis DM, Barr RM et al. Anti-FcεRI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol 1998: 102: 651–658.
35. Charlesworth EN, Hood AF, Soter NA et al. Cutaneous late-phase response to allergen: mediator release and inflammatory cell infiltration. J Clin Invest 1989: 83: 1519–1526.
36. Irani A-MA, Huang C, Xia H-Z et al. Immunohistochemical detection of human basophils in late-phase skin reactions. J Allergy Clin Immunol 1998: 101: 354–362.
37. Simons FER, Simons KJ. The pharmacology and use of H_1-receptor-antagonist drugs. N Engl J Med 1994: 330: 1663–1670.
38. Mason J, Reynolds R, Rao N. The systemic safety of fexofenadine HCl. Clin Exp Allergy 1999: 29(suppl 3): 163–173.
39. Gupta MA, Gupta AK, Ellis CN. Antidepressant drugs in dermatology: an update. Arch Dermatol 1987: 123: 647–652.
40. Bleehen SS, Thomas SE, Greaves MW et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomised double-blind study. Br J Dermatol 1987: 117: 81–88.
41. Bromm B, Scharein E, Darsow U et al. Effects of men-

thol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett 1995; 187: 157–160.
42. Lipworth BJ. Leukotriene-receptor antagonists. Lancet 1999; 353: 57–62.
43. Norris JG, Sullivan TJ. Leukotrienes and cytokines in steroid dependent chronic urticaria. J Allergy Clin Immunol 1998; 101(1 pt 2): S128.
44. Chu TJ, Warren MS. Zafirlukast (ACCOLATE®) in the treatment of chronic idiopathic urticaria—a case series. J Allergy Clin Immunol 1998; 101 (1 pt 2): S155.
45. Ohnishi-Inoue Y, Mitsuya K, Horio T. Aspirin-sensitive urticaria: provocation with a leukotriene receptor antagonist. Br J Dermatol 1998; 138: 483–485.
46. O'Donnell BF, Barr RM, Kobza Black A et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998; 138: 101–106.
47. Grattan CEH, Francis DM, Slater NGP et al. Plasmapheresis for severe, unremitting, chronic urticaria. Lancet 1992; 339: 1078–1080.
48. Barlow RJ, Kobza Black A, Greaves MW. Treatment of severe, chronic urticaria with cyclosporin A. Eur J Dermatol 1993; 3: 273–275.
49. Toubi E, Blant A, Kessel A et al. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. Allergy 1997; 52: 312–316.
50. Grattan CEH, O'Donnell BF, Francis DM et al. Randomised double blind study of cyclosporin A in chronic idiopathic urticaria. Br J Dermatol 2000; 143: 365–372.

Chronic Urticaria: Mechanisms and Treatment

Roger W. Fox, M.D.

ABSTRACT

Chronic urticaria (CU) is a vexing clinical syndrome. The clinician is challenged by the patient's symptoms. The experienced physician can evaluate the CU patient and prescribe effective treatment. The following review emphasizes the autoimmune mechanisms of CU. Despite this new insight into the pathogenesis of CU, many cases are still categorized as idiopathic. CU patients are a heterogenous group of patients who require an individualized approach to evaluation and management. (Allergy and Asthma Proc 22:97–100, 2001)

The cardinal clinical features of chronic urticaria (CU) are repeated occurrences of short-lived cutaneous wheals accompanied by redness and itching exceeding six weeks. Wheals are lesions ranging from a few millimeters to several centimeters in diameter. Individual groupings of urticaria may become confluent and develop into a large plaque. The individual wheals last less than 24 hours, with the exceptions of delayed pressure urticaria and urticarial vasculitis, which persist for 24–72 hours. Urticaria may occur anywhere on the skin, including the scalp, palms, and soles. There may be only one hive or a generalized outbreak. The itch of urticaria is the hallmark symptom, and it is usually worse in the evening or nighttime. CU typically follows this diurnal pattern. Angioedema (AE) accompanies 40–50% of the cases of chronic urticaria and 10% of the patients experience only AE without hives. AE is a manifestation of the same pathogenic process as urticaria. AE is a dermal, subcutaneous, or submucosal extravasation of plasma compared to the superficial dermal process in urticaria involving the post-capillary venules. Prominent AE may persist longer than 24 hours because of the time needed to resorb the tissue fluid. The sites of predilection for AE are dependent regions such as the hands, feet, genitals, face, eyelids, and lips. The alarming nature of oropharyngeal angioedema is rarely life-threatening in CU. AE does not itch; rather, the patient experiences burning or pain.[1]

Urticaria and angioedema are common cutaneous manifestations of many different disorders, and 20% of the general population experience hives some time in their lives.[2] Chronic urticaria occurs in 0.1% of the population;[3] when extrapolated to the U.S. population, 250,000 persons would have CU. Twenty percent of CU patients may be symptomatic over 20 years. The average duration of CU is about 3 to 5 years in adults, and a mean symptomatic period for CU of 6 months has been reported. Women are affected twice as often as men, and CU is uncommon in childhood.

The clinician can usually identify allergic type of urticaria, physical urticaria, and urticaria associated with connective tissue diseases by a thorough history and physical exam. The physical urticaria (cold, cholinergic, solar, dermatographia)[4] can be reproduced with the appropriate cutaneous stimulus and/or present at the time of the exam with the typical lesions. CU is rarely a manifestation of an allergic disorder, such as a 'hidden' food allergy or from a collagen vascular disease (systemic lupus or hypocomplementemic urticarial vasculitis (HUVS)).[5] Patients with CU are generally healthy and represent a heterogenous group of patients, some of whom experience mild symptoms while others have severe hives that are refractory to antihistamines and other commonly prescribed medications.

Most patients with CU are diagnosed with chronic idiopathic urticaria (CIU), which means that no cause can be identified. Recent research has discovered an IgG autoantibody directed against the alpha subunit of the high-affinity

From the Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Health Sciences Center, Tampa, Florida

Presented at Eastern Allergy Conference, Palm Beach, Florida, May 6, 2000

Address correspondence and reprint requests to Dr. Roger W. Fox, Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida Health Sciences Center, 13000 Bruce B. Downs Blvd., VAR 111D, Tampa, FL 63312

IgE receptor on the mast cell.[3] Less than 50% of CU patients have evidence of this autoimmune mechanism by immunoblot method or by a positive autogolous serum skin test (ASST). An anti-IgE antibody has been implicated in some CU patients. Twenty-five percent of CU patients have associated thyroid autoantibodies (anti-thyroglobulin and/or antiperoxidase).[6] The laboratory evaluation of CU patients is based upon the history and physical findings. The mainstay of CU treatment includes antihistamines, while some patients require additional therapy to suppress the manifestations. The focus of this review is on the current body of knowledge on the autoimmune mechanisms and the treatment of this vexing, mucocutaneous disorder.

CHRONIC URTICARIA; AUTOIMMUNITY

The histopathology of CU is different from acute urticaria (caused by an allergic reaction to a drug, venom, or food). In addition to the dermal edema seen in both types of urticaria, a mixed cellular perivascular infiltration of the dermal postcapillary venules is present in CU. The infiltration predominantly consists of CD4+ T cells and monocytes, with a prominent neutrophilic and/or eosinophilic infiltration in some cases.[7] The mast cell has a central role in the initiation of the process by releasing its mediators and cytokines and by activating and interacting with resident cutaneous cells and infiltrating cells. Epithelial (increased expression of TNF alpha), and endothelial cells (increased expression of adhesion molecules and IL3) play a supporting role in the pro-inflammatory process.[8] The infiltrating cells (T cells, monocytes, neutrophils, and eosinophils) amplify the urticaria response by releasing additional mediators, cytokines, and chemokines. CU represents a dynamic process involving a complex interplay of a number of cells, mediators, cytokines, chemokines, and adhesion molecules. The entire integument is activated in CU.

An initiating event for CU had been elusive, but in 1986 Grattan et al.[9] reported the presence of a serum factor that caused whealing on autologous intradermal injection or the ASST in some, but not all, patients with CU. In 1993, Greaves' laboratory identified this factor as an IgG with specificity for the alpha subunit of the high-affinity IgE receptor.[10] Subsequent studies have demonstrated this histamine-releasing receptor antibody as a causative factor in 30–45% of CU patients and another 5–10% have a pathogenic anti-IgE autoantibody. Anti-IgE receptor antibody is ubiquitous, and it is a nonpathologic antibody in several other cutaneous diseases and in normal controls. The IgG subtypes in CU are predominantly IgG1 and IgG3, both of which bind complement. Complement activation is required in CU along with the anti-IgE receptor antibody. The complement byproduct, C5a, is necessary for mast cell histamine release.[11] Only cutaneous mast cells have the receptor for C5a, explaining why mast cells in the lung or GI tract aren't activated in CU.

Less than 50% of CU patients react to an autologous serum skin test. Of these patients, 80% have a positive imumunoblot test demonstrating the presence of IgG to the alpha subunit of the IgE receptor. A histamine releasing factor (HRF) has been identified in the serum of CU patients, and HFR induces a wheal and flare response in some cases of CU.[12] Plasmapheresis removes the IgG anti-IgE receptor antibody, and results in temporary clinical improvement.[13] Intravenous gamma globulin induces a partial remission in CU, presumably by increasing the degradation of the pathogenic IgG.[14]

CHRONIC URTICARIA: URTICARIAL VASCULITIS

The incidence of chronic urticaria as a manifestation of a systemic connective tissue disease is <1%.[15] The most common immunologic disorders associated with urticarial vasculitis are serum sickness, chronic hepatitis C, HUVS,[16] and systemic lupus erythematosis (SLE). Immune complexes are deposited in the dermal post-capillary venules. Activation of the complement cascade results in the leukocytoclastic vasculitis changes in the skin (neutrophilic infiltration, nuclear debris, destructive changes of the involved venule). These patients are usually identified by the appearance and duration of the individual lesions (palpable purpura or persistent urticaria lasting 24–72 hours), associated hypocomplementemia, and elevated sedimentation rate. Other constitutional symptoms, such as fever or organ involvement (kidney, lung) are typical with these systemic disorders. Rarely, urticarial vasculitis can be an isolated manifestation involving only the skin. The histological findings of cutaneous vasculitis can usually be differentiated from the intense neutrophilic infiltration found in some patients with CU. The treating physician is concerned about missing the diagnosis of urticarial vasculitis, despite the rarity of these diseases causing chronic urticaria. Such physicians may order numerous, often unnecessary, laboratory studies (ANA, ESR, complement levels, hepatitis profiles). An extensive workup is indicated in the severe refractory cases of CU.

CHRONIC URTICARIA: THE THYROID CONNECTION

Seventeen to twenty-seven percent of euthyroid CU patients have thyroid autoantibodies (TA), antithyroglobulin, and/or anti-peroxidase.[6] TA are found in <6% of the general population. The precise role for these IgG autoantibodies in CU is unclear. Case reports of two CU patients have identified an IgE antibody for thyroid antigens which may be causative.[17] Thyroid hormone treatment has been reported to control the chronic urticaria in a small group of CU patients, although not all CU patients in the study responded to thyroid hormone. The thyroid autoantibody titers are not reduced by the thyroid hormone treatment. The association of thyroiditis, usually Grave's disease, with CU is cited in the literature. Not all patients' urticaria presenting with hyperthyroidism responds to treat-

ment of the underlying thyroid disorder. In addition, patients develop CU with a longstanding thyroid disorder who are stable on thyroid treatment, thus there appears to be no relationship between CU and TA in these cases.

Thirty-five percent of CU patients with a positive ASST have thyroid autoantibodies, whereas 15% of the CU patients without a positive ASST test positive for TA. In accordance with the proposed autoimmune basis of this subset of CU patients, a positive association with HLA-DR and -DQ alleles, known to be associated with autoimmunity, has been described.[18] Some experts believe that the observation of TA in some CU patients represents an unrelated, although parallel autoimmunity and the TA are only markers of autoimmunity.

CHRONIC URTICARIA: THE EVALUATION

Most CU patients are healthy individuals by history and physical exam, and no inciting cause is revealed by detailed questioning.[1] The CU patients are looking for answers to their chronic problem. Routine laboratory evaluations and vasculitis workups rarely uncover an etiology or change the treatment plan of the usual CU patient. Physical urticaria and urticarial vasculitis are diagnosed at the time of the physical exam by the experienced physician. There is no routine CU laboratory panel. A limited workup for CU can be ordered, which includes a CBC with differential, UA, ESR, and liver function studies. This approach may satisfy patients when they are told that "everything is normal." Specific studies can be ordered based on the clinical findings for vasculitis or hereditary angioedema. Food allergy tests or double-blind food/food additive provocation testing are rarely required in the CU patient, except in the rare case. Evaluations for chronic infections such as chronic sinusitis, *H. pylori, Trichophyton*, or *H. simplex* are futile endeavors.[3]

The typical CU patient should be screened for thyroid autoantibodies, and an autologous serum skin test can be easily done. In the refractory, severe CU patient, an autoimmune workup and skin punch biopsy are performed to evaluate for cutaneous vasculitis. For the angioedema-only patient who isn't taking an angiotensin converting enzyme (ACE) inhibitor, an evaluation for C1 esterase inhibitor (C1INH) deficiency is needed. Order quantitative and functional C1 INH, C1, C3, and C4 levels. Low or undetectable C1 INH and C4 make the diagnosis of hereditary angioedema. A low C1 level distinguishes the acquired type of C1 INH deficiency from the hereditary types of angioedema.[19]

CHRONIC URTICARIA: THE TREATMENT

The first prescription for all CU patients is an H1 antihistamine. The selection and dose of an H1 antihistamine depend upon the patient's response to the antihistamine. The ideal choice is an antihistamine that controls the pruritus and suppresses the wheal and flare without side effects. The less sedating antihistamines, Claritin, Allegra, and Zyrtec, are considered the first line treatments, since each is well tolerated at standard doses as well at higher doses that may be necessary for symptom control. For example, Allegra 60 mg b.i.d. may suffice, but Allegra 180 mg b.i.d. is recommended for the more refractory patient. Likewise, Claritin and Zyrtec are often prescribed at double the standard dose. Benadryl or hydroxyzine are commonly prescribed for the CU patient and each is effective, but sedation is a limiting factor. Hydroxyzine is often considered the drug of choice for CU in doses up to 50 mg every 6 hours. The physician may choose to prescribe a less sedating antihistamine in the morning and a sedating antihistamine in the evening. This combination achieves the desired goal of providing 24 hour antihistamine suppression of the symptoms with the fewest side effects. Another strategy is to give sedating antihistamines in low initial doses and gradually increase the dose until control of the hives is achieved. What is the optimal dose of an antihistamine or combination of antihistamines? The patient who doesn't respond to recommended doses or even double doses probably will not benefit by increasing the antihistamine dose or adding another antihistamine, particularly if the histamine skin test is suppressed by the prescribed antihistamine(s).

The physician at this point must decide whether to add another agent, such as an H2 antihistamine, or a leukotriene receptor antagonist (LTRA), Accolade or Singulair, to the H1 antihistamine. An H2 antihistamine improves the clinical course of a select few CU patients. The LTRAs have been reported to benefit small numbers of patients. Alternatively, the tricyclic antidepressant, Doxepin, is commonly prescribed when the above regimen have failed.[1] Doxepin is an excellent H1 and H2 antihistamine, but it is extremely sedating. Doxepin can be prescribed in the evening along with a less sedating antihistamine in the morning. As mentioned above, L-thyroxine may be used in the patient with demonstrable thyroid autoantibodies. An adequate trial with L-thyroxine for a month is recommended until the hives are controlled or until the TSH is suppressed. Corticosteroids are very effective in the management of severe CU, but the extended use of corticosteroids is not recommended due to their side effect profile. The exceptions to this rule are the severe cases of CU patients who require corticosteroids, because no other treatment has an impact on the clinical course. In these difficult cases all attempts to taper or to utilize alternate day corticosteroid therapy are mandatory. The experienced physician can utilize steroid-sparing agents in the severe CU patient. The drugs reported in the literature or in case studies include Dapsone, Plaquenil, Methotrexate, Stanazolol, and Cyclosporin. The response to each one of these drugs is unpredictable, and the side effects must be considered in the individual patient. The clinical experience with Cyclosporin is very encouraging. Cyclosporin in doses of 3.0–4.5 mg/kg have had good to excellent responses in two-thirds of patients who were treated for 3 months.[20] CU patients with anti-IgE receptor antibody have improved transiently after plasmapheresis and IV gamma globulin

infusions, but these treatments are expensive and unwarranted. Each clinical trial with a treatment plan should be carefully monitored for at least a month to determine whether a significant benefit can be determined. Fortunately, most CU patients are easily managed with antihistamines, but a select group of patients is much more difficult to manage, and present a frustrating experience for both the patient and the physician. Further evaluations of new treatments are needed before they can be generally accepted therapies for even the most severe CU cases. Future treatments will be guided by scientific discoveries on the molecular or cellular interactions involved in the pathophysiology in CU.

REFERENCES

1. Fox R. Urticaria and angioedema. Ch. 17. In Current Practice of Medicine: Allergy and Immunology. 2nd Ed. Lieberman PL (Ed.) Current Medicine, Inc., 141–150. 1998.
2. Champion R. H., Roberts S. O. B., Carpenter R. G., and Roger J. H. Urticaria and angioedema—a review of 554 patients. Br J Dermatol 81:588–597. 1969.
3. Greaves M. Chronic urticaria. J Allergy Clin Immunol 105:664–672. 2000.
4. Casale T. B., Sampson H. A., Hanifin J., et al. Guide to physical urticarias. J Allergy Clin Immunol 82:758–763. 1988.
5. Greaves M. W. Chronic urticaria. N Engl J Med 332:1767–1773. 1995.
6. Leznoff A., and Sussman G. L. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity—a study of 90 patients. J Allergy Clin Immunol 84:66–71. 1989.
7. Sabroe R. A., Poon E., Orchard G. E., et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. J Allergy Clin Immunol 103:484–493. 1999.
8. Hermes B., Prochazka A. K., Haas N., et al. Upregulation of TNF-α and IL-3 expression in lesional and uninvolved skin in different types of urticaria. J Allergy Clin Immunol 103:307–314. 1999.
9. Grattan C. E. H., Wallington T. B., Warin R. P., et al. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. Br J Dermatol 114:583–590. 1986.
10. Hide M., Francis D. M., Grattan C. E. H., and Greaves M. W. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. N Engl J Med 328:1599–1604, 1993.
11. Ferrer M., Nakazawa K., and Kaplan A. P. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol 104:169–172, 1999.
12. Fagiolo U., Cancian M., Bertollo L., et al. Inhibitory effect of heparin on skin reactivity to autologous serum in chronic idiopathic urticaria. J Allergy Clin Immunol 103:1143–1147. 1999.
13. Grattan C. E. H., Francis D. M., Slater N. G. P., et al. Plasmapheresis for severe unremitting chronic urticaria. Lancet 339:1078–1080, 1992.
14. O'Donnell B. F., Barr R. M., Blac A. K., et al. Intravenous immunoglobulin in chronic autoimmune urticaria. Br J Dermatol 138:101–106, 1998.
15. Tong L. J., Balakrishran G., Kochan J. P., et al. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 94:461–465, 1997.
16. Wisnieski J. J., Baer A. N., Christensen J., et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serological findings in 18 patients. Medicine 74: 24–41, 1995.
17. Bar-Sela S., Reshef T., and Mekori Y. A. IgE antithyroid microsomal antibodies in a patient with chronic urticaria. J Allergy Clin Immunol 103: 1216–1217, 1999.
18. O'Donnell B. F., O'Neill C. M., Francis D. M., et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br J Dermatol 140: 853–858. 1999.
19. Markovic S. N., Inwards D. J., Frigas E. A., and Phyliky R. P. Acquired C1 esterase inhibitor deficiency. Ann Intern Med 132:144–150, 2000.
20. Grattan C. E. H., O'Donnell B. F., Francis D. M., et al. Randomised double-blind study of cyclosporin in chronic idiopathic urticaria. Br J Dermatol, in press. □

Natural course of physical and chronic urticaria and angioedema in 220 patients

Martina M. A. Kozel, MD,[a] Jan R. Mekkes, MD, PhD,[a] Patrick M. M. Bossuyt, PhD,[b] and Jan D. Bos, MD, PhD[a] *Amsterdam, The Netherlands*

Background: Information about spontaneous remission of chronic urticaria is limited.

Objective: To investigate the natural course of urticaria, we followed up 220 adults in a prospective study.

Methods: Patients were followed up for 1 to 3 years to evaluate interventions, to detect latent causes, and to study the natural course of urticaria. The diagnosis was made by detailed history-taking as well as laboratory and provocation tests.

Results: Thirty-five percent of all patients were free of symptoms after 1 year. In 28.9% of patients, symptoms had decreased. Spontaneous remission occurred in 47.4% of the patients in whom no cause of their urticaria and/or angioedema could be identified and in only 16.4% of the patients with physical urticaria. A cause could be identified in 53.1% of the patients. Thirty-six percent of the patients had idiopathic urticaria. Chronic idiopathic urticaria combined with physical urticaria occurred in 10.9%.

Conclusion: In general, the prognosis for spontaneous remission is reasonable, with the exception of the subgroup (33.2%) with physical urticaria. (J Am Acad Dermatol 2001;45:387-91.)

Urticaria is characterized by a well-demarcated eruption of transitory, usually itchy, and sometimes even painful erythematous skin swellings that can recur for months or years. Previous investigators have defined chronic urticaria as episodes recurring for more than 6 weeks.[1] Urticaria and angioedema are common disorders.[2] Approximately 5% of patients with a bout of urticaria will be symptomatic for longer than 4 weeks.[3] Thirty percent of patients with urticaria seen in a family practice have chronic urticaria.[3] In clinical studies percentages of causes found for urticaria vary between 20% and 90%.[2,4-7] The percentages of found causes differ because different inclusion and exclusion criteria (eg, inclusion of physical urticarias) were used.

From the Departments of Dermatology[a] and Clinical Epidemiology and Biostatistics,[b] Academic Medical Center, University of Amsterdam.

Supported by the Guidelines Development Program of the Academic Medical Center of the University of Amsterdam.

None of the authors has had commercial associations, current or during the past 5 years, that might pose a conflict of interest.

Accepted for publication April 4, 2001.

Reprints not available from authors.

0190-9622/2001/$35.00 + 0 **16/1/116217**

doi:10.1067/mjd.2001.116217

Chronic urticaria may be caused by internal diseases or malignancies, but these underlying diseases are rarely found.[2,4,8-10] In the past, extensive laboratory screening has been performed to exclude an underlying disease. Recent diagnostic guidelines recommend thorough history-taking and only a very limited amount of laboratory tests.[11,12] In a prospective study we evaluated the benefit of extensive laboratory testing and concluded that tests not based on the history do not contribute to the detection of underlying causes of chronic urticaria.[13] This study was performed in the same patient cohort.

Very little is known about the natural course of chronic idiopathic or physical urticaria. A literature search including articles from 1966 to 2000 revealed more than 5500 medical articles on urticaria or angioedema (or both), but only 13 articles referred to the natural course of the disease.

The aim of this prospective cohort study in consecutive patients was to investigate the natural course and prognosis of chronic urticaria and/or angioedema, including subtypes such as physical urticaria.

SUBJECTS AND METHODS

Patient recruitment, patient population, and study design

The study was performed at the outpatient Department of Dermatology of the Academic

Medical Center in Amsterdam, The Netherlands, which is a secondary and tertiary care center. From January 1992 to July 1994, all consecutive patients older than 15 years with urticaria and/or angioedema of unknown origin and with at least a 6-week duration of the symptoms were included.

Two hundred twenty patients were investigated. One hundred thirty-two women and 88 men were enrolled in the study; their mean age was 38 years (range, 15-79 years). Forty-one patients (19%) had urticaria only, 64 patients (29%) had urticaria and angioedema, and 18 patients (8%) had angioedema without urticaria.

After informed consent had been obtained, the patients were subjected to a diagnostic protocol, which included a detailed questionnaire, physical examination, laboratory tests, provocation tests for physical urticaria, and adverse reactions to food and drugs. The protocol was approved by the Medical Ethical Committee.

Patient questionnaire

A detailed history was obtained from all patients, using a standardized questionnaire with particular attention to possible causes of urticaria, based on earlier published questionnaires[14-16] and personal experiences.

Laboratory investigations and provocation tests

The study was part of a research project for the development of evidence-based clinical guidelines for laboratory investigations in patients with chronic urticaria and/or angioedema.[13] Therefore many hematologic, immunologic, biochemical, and allergy tests; cultures; and x-rays were performed, as described in detail elsewhere.[13] Provocation tests for physical urticaria were performed.[17,18] To evaluate dermographism, firm stroking of the skin was performed, which induces itchy, linear hives within minutes. The test for pressure urticaria was performed with a special device that applied 3 different weights on the back of the patient for 20 minutes; the appearance of whealing was checked for during the day. Cold urticaria was tested with a steel container with ice cubes applied to the forearm for 20 minutes. Cholinergic urticaria was provoked by a hot shower or exercise until sweating. Screening for food allergy or intolerance was investigated by an elimination diet for at least 3 weeks. All drugs used were discontinued or replaced with chemically unrelated equivalents. Drug provocation tests and oral food rechallenge tests were performed if necessary.

Follow-up

After a follow-up period of at least 1 year, patients were asked whether they had remaining or new complaints and whether they still used antihistamines, oral corticosteroids, or other drugs. Laboratory tests were repeated, if indicated. The follow-up was directed at detecting causes of urticaria not traced initially by the questionnaire, to evaluate the effect of interventions, and to obtain information about the natural course of the different subtypes of urticaria.

RESULTS

Patient questionnaire

Twenty-five percent of the patients had urticaria continuously, 30% of them had daily bouts, 22% had more than 2 bouts every week, and the remaining group less frequently had hives or only angioedema. In 94% of the patients the itch was the most important complaint. Sleeping disorders occurred in 25% of the patients with urticaria and in 4% of the patients with angioedema. Twenty-eight percent of the patients reported intense pruritic whealing from insect bites or stings. This was mainly seen in patients with chronic urticaria and urticaria factitia. Occurrence of urticaria in the family (parents, siblings, grandparents, aunts, uncles, cousins, or nieces) was reported by 10% of the patients, angioedema by 6%, and allergies (not further specified) by 45%. A history of atopy was reported in 40% of the study population.

A large percentage of the patients mentioned that factors such as stress (36%), warm environment (23%), dermographism (13%), and consumption of alcohol (9%) or analgesic drugs (8%) aggravated their urticaria.

Laboratory investigations and provocation tests

In 89% of the patients no abnormalities were found during the physical examination. Dermatologic problems (eg, tinea pedis, vaginal discharge, lipoma, different forms of eczema, acne, or folliculitis) were found and treated in 19 patients. Three patients had emphysema and 2 had arterial insufficiency of the lower legs.

In patients with more than one type of physical urticaria, the type which interfered most with normal life was used for the classification. Of all patients, 10.9% had a combination of physical urticaria and urticarial lesions of unknown origin. In Table I we described this group of patients as having a combination of (one type of) physical urticaria and idiopathic urticaria.

After discontinuation of suspected drugs, provocation tests were performed by reintroducing the drug in a symptom-free period, which resulted in a relapse of symptoms in all patients. The responsible drugs are listed in Table I.

In two patients exercise-induced, food-dependent urticaria was found. In both patients consumption of

J Am Acad Dermatol
Volume 45, Number 3

Table I. Causes of physical urticaria (PU), chronic urticaria (CU), and/or angioedema (A) and type of reaction in 220 patients

	No. of patients	% Study population	Type of reaction
Physical urticaria	73	33.2	
Dermographism	37	16.8	PU
Pressure	7	3.2	PU
Cold	11	5.0	PU, PU + CU + A
Cholinergic	11	5.0	PU
Heat contact	1	0.5	PU
Solar	4	1.8	PU
Exercise-induced	2	0.9	CU + A
Combination of physical urticaria and chronic idiopathic urticaria	24	10.9	
Dermographism	10	4.5	PU + CU
Pressure	13	5.9	PU + CU
Cold	1	0.5	PU + CU
Drugs	20	9.0	
Aspirin	5	2.3	PU + CU, CU, A
NSAIDs	3	1.4	CU + A, A
Codeine	1	0.4	CU + A
Propyphenazone	2	0.9	PU + CU, A
Antibiotics	3	1.4	PU + CU, CU, A
Antidepressants	1	0.4	PU
ACE inhibitors	2	0.9	A
Oral contraceptives	2	0.9	CU + A
Methotrexate	1	0.4	CU
Food	15	6.8	
Normal hives and/or angioedema	10	4.5	CU + A, CU, A
Dermographism	3	1.4	PU
Exercise-induced, food-dependent	2	0.9	CU + A
Infections	4	1.8	PU, CU
Internal diseases	3	1.4	CU, CU + A
Contact urticaria	2	0.9	CU
Malignancies	0	0	
Hereditary angioedema	0	0	
Chronic idiopathic urticaria	78	36.0	CU + A, CU, A

ACE, Angiotensin-converting enzyme; *NSAID,* nonsteroidal anti-inflammatory drugs.

cereals in combination with exercise resulted in urticaria and angioedema; radioallergosorbent tests (RASTs) to cereals were positive, and provocation tests confirmed the diagnosis. In two patients urticaria factitia developed after consumption of food containing vasoactive amines (eg, wine and cheese). RASTs were negative. One patient with severe hay fever had complaints of urticaria factitia after consuming apples and tomatoes. These 3 causes were found by means of the elimination diet followed by reintroduction of the particular food. Three patients developed severe reactions (eg, syncope and shock) after consuming crustaceans (in one patient), flour (in one), and sesame oil (in one). Scratch tests were highly positive and the oral allergy syndrome was present. Provocation tests would have been dangerous, and the patients were not willing to participate. In 7 patients, after following the elimination diet and a period of food reintroduction, the following foods were found to be the most likely cause of the urticaria and/or angioedema: dairy products (3 times), eggs (1 time), alcohol (1 time), beef (1 time), and apples/pears (1 time). In one patient the specific RAST was positive (apple/pear). Continuation of the diet resulted in disappearance of the complaints and by reintroduction of the particular food, hives occurred.

In 4 of 10 patients with a parasitic infection, the complaints disappeared after treatment. Their complaints were urticaria factitia and pruritus, not classic hives or angioedema. In two patients an infection with *Trichuris trichiura* and in two other patients an infection with *Strongyloides stercoralis* were found. These patients were born or had lived for a long period in a tropical country.

Table II. Percentages of patients free of symptoms after 1 year

Idiopathic, all patients	47.4% (37/78)
Urticaria only	38.5% (10/26)
Angioedema only	20.0% (2/10)
Both urticaria and angioedema	59.5% (25/42)
Physical and idiopathic urticaria	20.8% (5/24)
Physical urticarias	16.4% (12/73)

The following internal diseases, probably related to the urticaria, were found: Sjögren's syndrome, systemic lupus erythematosus, and paraproteinemia. Hives are still present in them after 3 years' follow-up. Histopathologic evaluation of the skin biopsy specimens did not reveal urticarial vasculitis in this cohort, even in patients who had mentioned that they had wheals for longer than 48 hours. No other severe internal disease or malignancy associated with urticaria or angioedema was found.

Contact urticaria to latex and preservatives was found in two patients.

Follow-up

Follow-up data were obtained by interviewing the patient at the outpatient department, by telephone inquiry, or, in 3 cases, by contacting the general practitioner. The mean follow-up period was 2 years 4 months (range, 12-71 months). One patient was followed up for only 3 months because he moved. In this patient no cause of urticaria could be identified.

Ninety percent of the patients used nonsedating antihistamines during follow-up, 46% used sedating antihistamines as well, 16% occasionally used systemic prednisolone during severe bouts, and in 4% of the patients epinephrine for intramuscular use was prescribed.

After 3 months 14% of the 220 patients were free of complaints. After 6, 9, and 12 months, 26%, 30%, and 35%, respectively, were free of symptoms. At the end of the follow-up period, in 28.9% of the patients the symptoms had decreased, in 35% the symptoms remained the same, and in 1.4% the symptoms had worsened. In 25% of the 220 patients, a spontaneous remission occurred after 1 year.

For the entire patient group with idiopathic urticaria and/or angioedema, as well as for the different subtypes (idiopathic urticaria only, idiopathic angioedema only, idiopathic urticaria and angioedema, physical urticaria, and combination of physical and idiopathic urticaria), we investigated the number of patients who were free of symptoms after 1 year (Table II). In some patients with physical urticaria, a parasitic infection or an adverse event to food or drugs was provoking dermographism. These patients were not included in Table II.

DISCUSSION

This study provides information about the natural course of different types of urticaria. In a disease in which it is often not possible for the clinician to determine the cause of patients' complaints, it is helpful to be able to inform them about their prognosis. In this study, 47.4% of the patients with idiopathic urticaria and/or angioedema were free of symptoms after 1 year, and only 16.4% of the patients with physical urticaria were free of symptoms.

A limitation of this study is that it was performed in a secondary and tertiary care center, and the results may not be applicable to other patient populations. Furthermore, by analyzing the number of patients with different forms of urticaria separately, the percentages are based on smaller numbers of patients.

An advantage of the study design is that we followed a well-defined cohort of 220 patients. A cohort study is considered to be the best study design to identify prognostic factors and to determine the relationship between a prognostic factor and disease duration.[19]

We performed extended laboratory investigations not because we believed that they are necessary to detect the cause of chronic urticaria, but to provide evidence that routine investigations are not useful if performed without an indication from history-taking or a questionnaire. This hypothesis could be confirmed and was presented in another article.[13]

Only a few studies deal with the natural course of chronic urticaria. Urbach[20] found in 500 patients with urticaria and/or angioedema the following percentages of durations: 3 to 12 months (19%), 1 to 5 years (20%), 6 to 10 years (4%), and after 11 to 20 years (1.5%). Humphreys and Hunter[7] found that symptoms were present for more than 5 years in 5% of the patients when they first attended a general dermatology clinic and in 13% of patients who visited a specialized urticaria clinic. Quaranta et al[21] investigated 86 patients with chronic idiopathic urticaria in whom 27 (31%) resolved, 48 (56%) continued to have symptoms, and in 11 (13%) the natural cause was unknown. It made no difference whether the patients had urticaria, angioedema, or urticaria and angioedema. In 32% of their patients, complaints resolved after a 3-year period. In our patient cohort, 47.4% of this subgroup of patients (having idiopathic urticaria and/or angioedema) were free of symptoms after 1 year. Information on the natural course of chronic urticaria in a large group of patients was given by Champion et al[2] in 1969. In their study approximately 45% of patients with idiopathic urticaria only still had com-

plaints after 1 year. In our study group 61.5% of the patients with idiopathic urticaria only still had complaints. Champion et al found that for patients with idiopathic angioedema only and for patients with idiopathic urticaria and angioedema, about 55% and 70%, respectively, still had symptoms after 1 year. We found this in 80% and 40.5% of our patients with idiopathic angioedema only and with idiopathic urticaria and angioedema, respectively. We could not confirm that patients with idiopathic urticaria and angioedema had the worst prognosis. In our study physical urticaria was the worst prognostic factor; 84% of the patients still had complaints after 1 year.

In many of the previously published studies the percentages of identified causes are smaller than in our study.[2,4] In particular, the number of physical urticaria cases is high, probably because efforts were made to detect them with detailed questions and provocation tests. Physical urticaria was found in 12% to 57% of patients in different studies in the literature from 1937 to 1985, including 120 to 500 patients, depending on the care center.[22]

In 3.6% of the patients the urticaria was caused by medication and not by the internal disease or infection for which the drugs were prescribed. One patient had a mesothelioma, but his angioedema was not related to his malignancy and it cleared after discontinuing medication.[23] In another patient with severe rheumatoid arthritis, methotrexate induced the urticaria. In some patients exacerbation occurred during viral infections. This was often related to the use of analgesic drugs.

An elimination diet followed by reintroduction of the food was helpful in a few patients motivated to find a cause, but the frequency of food reaction was very low. During the follow-up period all found infections (parasite infections, vaginitis, or cystitis) were treated, and only in 4 patients with a parasitic infection was there a probable relation with urticaria factitia.

In conclusion, spontaneous remission occurs in approximately 47% of the patients with chronic idiopathic urticaria and/or angioedema within 1 year after referral. Only 16% of the patients with physical urticaria were free of symptoms after 1 year. In patients referred to a tertiary care center for chronic urticaria, the prognosis is reasonable. This is another argument for adopting an attitude of waiting regarding extensive laboratory screening.

REFERENCES

1. Henz BM. The spectrum of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic Aspects. Berlin: Springer-Verlag; 1998. p. 3.
2. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema: a review of 544 patients. Br J Dermatol 1969;81:588-97.
3. Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter- and episode- and process-oriented standard output from the Transition Project. Parts 1 and 2. Amsterdam: Amsterdam University Press; 1991.
4. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119: 427-36.
5. Zuberbier T, Chantraine-Hess S, Hartmann K, Henz BM. Pseudoallergen-free diet in the treatment of chronic urticaria: a prospective study. Acta Derm Venereol 1995;75:484-7.
6. Henz BM, Zuberbier T. Causes of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer-Verlag; 1998. p. 29.
7. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-8.
8. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-81.
9. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol 1990;123:453-6.
10. McWhorter WP. Allergy and risk of cancer: a prospective study using NHANESI follow-up data. Cancer 1988;62:451-5.
11. Friedman PS. Assessment of urticaria and angio-oedema. Clin Exp Allergy 1999;29:109-12.
12. Bindslev-Lensen C, Finzi A, Greaves M, Camarasa J, Ortonne JP, Schöpf E, et al. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol Venereol 2000;14:175-80.
13. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-80.
14. Gross AS, LaTour DL, King LE. Chronic urticaria: a model questionnaire for patient screening. Cutis 1990;46:421-4.
15. Guin JD. The evaluation of patients with urticaria: symposium on urticaria and the reactive inflammatory vascular dermatoses. Dermatol Clin 1985;3:31-6.
16. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer- Verlag; 1988. p. 183-9 (Appendix A).
17. Kontou Fili K, Borici-Mazi R, Kapp A, Matjevic LJ, Michel FB. Physical urticaria: classification and diagnostic guidelines: an EAACI position paper. Allergy 1997;52:504-13.
18. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer-Verlag; 1998. p. 193-5 (Appendix C).
19. Laupacis A, Wells G, Richardson S, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. JAMA 1994;272:234-7.
20. Urbach E. In: Urbach E, Gottlieb PM. Allergy. 2nd ed. New York: Grune and Stratton; 1946.
21. Quaranta JH, Rohr AS, Rachelefsky GS, Siegel SC, Katz RM, Spector SL, et al. The natural history and response to therapy of chronic urticaria and angioedema. Ann Allergy 1989;62:421-4.
22. Paul E, Greilich KD. Zur Epidemiologie der Urtikariaerkrankungen. Hautarzt 1991;42:366-75.
23. Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. Clin Exp Dermatol 1995;20:60-1.

British Journal of Dermatology (1990) **123**, 453–456.

Chronic urticaria and cancer: an epidemiological study of 1155 patients

B.LINDELÖF, B.SIGURGEIRSSON, C.F.WAHLGREN AND G.EKLUND*

Departments of Dermatology and *Cancer Epidemiology, Karolinska Hospital, Stockholm, Sweden

Accepted for publication 25 April 1990

SUMMARY

To evaluate the possible association of malignant disease with chronic urticaria 1155 consecutive cases with chronic urticaria were reviewed. The Swedish Cancer Registry, Stockholm, was searched for records reporting malignancies in the study population (1958–84), and the expected number of malignancies was calculated on the basis of age- and sex-standardized incidence data. A malignancy was diagnosed in 36 patients with urticaria and the expected number of malignancies was 41. In 23 patients the malignancy appeared during the same year as the onset of urticaria or later. The expected number was 25·6. We conclude that chronic urticaria is not statistically associated with malignancy in general.

Many dermatoses have been considered to be related to an underlying internal malignancy.[1] Urticaria and angio-oedema have been reported mainly in association with lymphoproliferative disorders.[2–16] However, not every dermatosis occurring in a patient suffering from malignant disease is causally related. When the dermatosis is common, as with urticaria, the possibility increases that the association has occurred only by chance. We investigated the incidence of cancer in a large number of patients with chronic urticaria and related the observed number of malignancies to the number expected, in a contemporary population with the same age and sex distribution. The incidence of cancers as well as the expected number of cancers were obtained from the Swedish Cancer Registry, Stockholm.

METHODS

Patients

During the years 1968–83, 1155 patients with chronic urticaria were seen at the Department of Dermatology, Karolinska Hospital, Stockholm. All had had symptoms for more than 3 months. The patients consisted of 704 females and 451 males (median age 32 years, age range 1–85 years) (Fig. 1). The follow-up period was on average 8·2 years.

Correspondence: Dr B.Lindelöf, Department of Dermatology, Karolinska Hospital, S-104 01 Stockholm, Sweden.

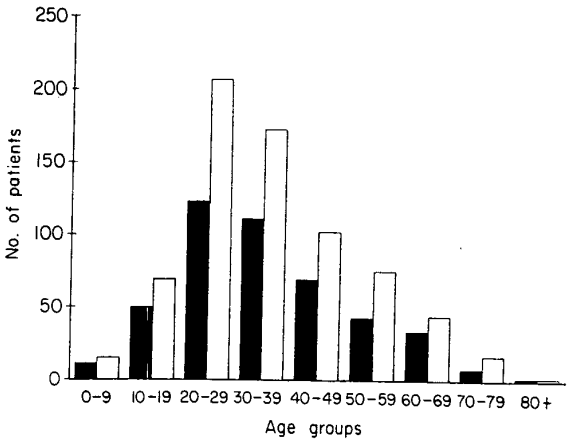


FIGURE 1. Age distribution of 1155 patients with chronic urticaria. ■, males; □, females.

Swedish Cancer Registry

Information from the Swedish Cancer Registry, Stockholm, (1958–84) and the 1155 patients was correlated to identify individuals with malignant tumours. Nationwide information on the cancer incidence in Sweden is available from 1958, when compulsory registration was begun. The registry collects information on diagnosed cancers from both clinicians and pathologists so that most cases are reported by two sources. Each patient is characterized by a unique identification number composed of six digits based on year, month, and day of birth, supplemented with a registration number (three digits) and a check digit. Therefore, the identification numbers are not affected by the possibility of changes in names. The completeness of registration in the Swedish Cancer Registry has been found to be 96–97% for all cancers.[17]

Statistics

The expected number of malignant tumours was estimated on the basis of incidence data from the Swedish Cancer Registry, Stockholm.[18] The age- and sex-specific cancer incidence was calculated as a national average for 1971–84. The incidence rates were assumed to be constant within 5-year age and calendar-time intervals. Regional differences were disregarded. To allow for deaths occurring during the observation period, deductions were made on the basis of life tables for the whole Swedish population. To derive the expected number of malignant tumours, the number of person years at risk in each group was multiplied by the sex-specific and age-specific cancer incidence for the relevant 5-year period. The number of person-years of observation was calculated separately for each sex and amounted to 9400. After the ratio between observed and expected number of malignancies had been estimated, significance and confidence interval analysis was performed using the Poisson distribution.

RESULTS

A malignant tumour was diagnosed in 36 patients with urticaria. The expected number was 41 and thus the relative risk was 0·88, confidence interval 0·61–1·22. Of these patients with malignancy, 23 cancers appeared during the same year as the onset of urticaria or later. The

TABLE 1. Observed and expected number of malignancies in 1155 patients with chronic urticaria

	Number of malignancies	
	Observed	Expected
All patients ($n = 1155$):		
Females ($n = 23$)	23	26·8 NS
Males ($n = 13$)	13	14·2 NS
Total	36	41·0 NS
Cancer the same year as onset of urticaria or later		
Females ($n = 14$)	14	15·7 NS
Males ($n = 9$)	9	9·9 NS
Total	23	25·6 NS

NS, not significant.

TABLE 2. Characteristics of 10 patients with chronic urticaria associated with malignancy (cancer within 5 years after onset of urticaria)

		Age at onset (years) of		
Case	Sex	Urticaria	Malignancy	Type of malignancy
1	M	79	83	Rectum
2	M	69	73	Rectum
3	M	67	71	Colon
4	M	69	72	Stomach
5	M	60	63	Malignant melanoma
6	M	47	52	Skin, squamous cell carcinoma
7	F	61	65	Ovary
8	F	58	60	Corpus uteri
9	F	48	49	Glioblastoma
10	F	78	79	Malignant lymphoma

expected number was 25·6. These differences are not statistically significant (Table 1). Characteristics of those 10 patients who had their malignancy the same year or within 5 years after onset of urticaria are given in Table 2. The study population is shown in Figure 1.

DISCUSSION

This study strongly suggests that chronic urticaria is not statistically associated with malignancy. The study population is well defined and the number of observed and expected cancers are reliable owing to the accurate population statistics used in Sweden.

The link between skin markers and underlying malignant disease has always interested dermatologists. If an association between a skin lesion and internal malignancy has been

suggested, the dermatologist has to decide whether there is a need for investigation. If so, how extensive should a search be and how often should the search be repeated? The patient may undergo unnecessary procedures with both socioeconomic and psychological consequences, particularly if the association is false. If the suggested cutaneous sign is common and chronic, because internal malignant diseases are often chronic, it is easy to find patients with both conditions at the same time, as illustrated in Table 2. Therefore, the only way to prove an association of a common skin condition with internal malignancy is to perform a large and controlled study. If, however, the dermatosis is uncommon, e.g. erythema gyratum repens, case reports are the basis for the association as large studies cannot be carried out. We conclude that the hypothesis that urticaria is associated with internal malignant disease was based on case reports only, and this large-scale study has shown that this association probably occurred by chance.

REFERENCES

1 Haynes HA, Curth HO. Cutaneous manifestations associated with malignant internal disease. In: *Dermatology in General Medicine* (Fitzpatrick TB *et al.*, eds), 2nd edn. New York: McGraw-Hill Company, 1979.

2 Hills EA. Adenocarcinoma of the bronchus with Cushing's syndrome, carcinoid syndrome, neuromyopathy and urticaria. *Br J Dis Chest* 1968; **62:** 88–92.

3 Ross TF, Coleman DL, Naughton JL. Angioedema and small-cell carcinoma of the lung. *Thorax* 1982; **37:** 950–1.

4 Lewkonia RM, Pineo GF. Angioedema-like skin lesions associated with lymphoproliferative disease. *Can Med Assoc J* 1982; **127:** 867–8.

5 Gottlieb M, Campbell K, Pelzmann, K, Hu C-H. Long-standing angioedema with C1-esterase inhibitor deficiency associated with occult lymphoma. *West J Med* 1983; **138:** 258–60.

6 Fiechtner JJ, Marx JJ, Wolski KP, Schloesser LL. Acquired angioedema, autoimmune hemolytic anemia and lymphoma: resolution after therapy. *Clin Immunol Immunopath* 1980; **15:** 642–5.

7 Vallent K, Fehér J, Somogyi A, Joós A. Angioneurotic oedema and hypocomplementaemia in patients with thyroid cancer. *Acta Chir Acad Scien Hungaricae* 1982; **23:** 163–170 (Ger).

8 Highet AS. Urticaria vasculitis and IgA myeloma. Eastern Counties Dermatological Society March 1979. Society Proceedings. *Br J Dermatol* 1980; **102:** 355–7.

9 Jones L, Bubel MA, Newland, AC. C1 esterase inhibitor as a possible tumour marker in malignant lymphoma. *Clin Lab Haemat* 1985; **7:** 279–81.

10 Stockley RJ, Daneshmend TK. Painful urticaria heralding the appearance of Philadelphia chromosome positive acute myeloid leukaemia. *Clin Lab Haemat* 1986; **8:** 161–4.

11 Gordon EH, Beall GN, Klaustermeyer WB. Angioedema and multiple myeloma. *Ann Allergy* 1983; **51:** 349–50.

12 Hasegawa J, Ke M. Cold urticaria, cryoglobulinemia and ? myeloma. *Arch Dermatol* 1970; **101:** 239–41.

13 Ben-Chetrit E, Stern Z, Polliack A. Cold urticaria: an unusual manifestation of histiocytic lymphoma. *Acta Haemat* 1982; **68:** 343–4.

14 Rawnsley HM, Shelley WB. Cold urticaria with cryoglobulinemia in a patient with chronic lymphocytic leukemia. *Arch Dermatol* 1968; **98:** 12–17.

15 Bonvalet D, Foldes C, Civatte J. Cutaneous manifestations in chronic lymphocytic leukemia. *J Dermatol Surg Oncol* 1984; **10:** 278–82.

16 Lindelöf B, Wahlgren C-F. Chronic urticaria associated with internal malignancy. *Int J Dermatol* 1990; **29:** 384.

17 Mattsson B. Cancer registration in Sweden. Studies on completeness and validity of incidence and mortality registers. *Thesis*. Karolinska Institute, Stockholm, 1984; 1–33.

18 Adami H-O, Gunnarson T, Sparén P, Eklund G. The prevalence of cancer in Sweden 1984. *Acta Oncologica* 1989; **28:** 463–70.

Current reviews of allergy and clinical immunology
(Supported by a grant fromAstra Pharmaceuticals, Westborough, Mass)

Series editor: Harold S. Nelson, MD

Chronic urticaria

Malcolm Greaves, MD *London, United Kingdom*

Chronic urticaria remains a major problem in terms of etiology, investigation, and management. It is important to identify patients in whom physical urticaria is the principal cause of disability. Once confirmed by appropriate challenge testing, no further investigation is required. Urticarial vasculitis (UV) is a major differential diagnosis of "idiopathic" urticaria (CIU). I perform biopsy of most patients in this category because UV cannot be considered confirmed in the absence of histologic evidence. Patients with confirmed UV need to be thoroughly investigated for paraproteins, lupus erythematosus hepatitis B and C, and inflammatory bowel disease. Of patients with CIU, a few (<5%) prove to have food additive reactivity confirmed by placebo-controlled challenge testing. There is no convincing evidence of the involvement of *Helicobacter pylori* or parasite infestation as a cause of chronic urticaria, although *H pylori* could have an indirect role. Recently it has become clear that 27% to 50% of patients with CIU have functional autoantibodies directed against the α-chain of the high-affinity IgE receptor or less commonly against IgG. These antibodies, whose involvement has now been independently confirmed in several centers, are identified by autologous serum skin testing and confirmed by histamine release studies or immunoblotting. Their removal (by intravenous Ig or plasmapheresis) or treatment by cyclosporine has proved highly beneficial in severely affected patients. However, the routine treatment of all CIU patients, irrespective of etiology, remains the judicious use of H_1 antihistamines. (J Allergy Clin Immunol 2000;105:664-72.)

Key words: Chronic urticaria, immunology, allergy, urticarial vasculitis, idiopathic urticaria, intravenous Ig, itching, cold urticaria

Recently, new light has been shed on the pathomechanisms of so-called chronic "idiopathic" urticaria (CIU), and this has in turn led to new approaches to diagnosis and, at least for some patients, treatments. However, it has to be admitted that, in many patients with chronic urticaria, the etiology still remains unclear despite our best efforts and these patients have to be managed symptomatically.

Abbreviations used
CIU: Chronic idiopathic urticaria
FcεRI: High-affinity receptor for IgE
UV: Urticarial vasculitis

CLINICAL FEATURES OF CHRONIC URTICARIA

The cardinal clinical features of urticaria that distinguish it from any other type of inflammatory eruption are the repeated occurrence of short-lived cutaneous wheals accompanied by redness and itching (Fig 1). Wheals are lesions ranging from a few millimeters to several centimeters in diameter, although if they run together and become confluent much larger plaques may occur. Individual wheals normally, by definition, last less than 24 hours, although there are exceptions. Wheals of the physical urticaria–delayed pressure urticaria may individually last for as long as 48 hours and the wheals of urticarial vasculitis (UV) by definition should last in excess of 24 hours. Urticarial wheals are generally paler than the bright red of the surrounding skin because of the compressing effect of dermal edema on the normally blood-engorged postcapillary venules. The surrounding skin may sometimes be conspicuously pale rather than red, giving the impression of a white halo. This phenomenon, more common in acute physical urticarias such as cholinergic urticaria and in acute allergic urticarias, is the result of a "steal" effect, increased arteriolar blood flow associated with the central wheal leading to deprivation of blood flow in the perilesional skin. Wheals may be round or irregular with pseudopodia.

Urticaria may occur anywhere on the skin, including the scalp, palms, and soles. Unlike angioedema, urticaria of the mucous membranes is rare, although the physical urticaria–cold urticaria may involve the tongue or palate.

The itch of urticaria is almost invariable, although some patients may have more intense pruritus than others. Qualitatively, the itching may be pricking or burning in quality. It is usually worse in the evening or nighttime[1] and is relieved by rubbing the skin rather than by scratching: heavily excoriated skin is rarely if ever a consequence of urticaria.

At least 50% of patients with chronic urticaria also have angioedema.[2] Angioedema can be defined as short-lived deep dermal and subcutaneous or submucosal edema. Like the wheals of urticaria, the swellings of angioedema normally last less than 24 hours, but large swellings tend to last longer. Disfiguring when they

From St John's Institute of Dermatology, St John's Hospital, United Medical and Dental School, London, United Kingdom.
Received for publication Dec 3, 1999; revised Jan 14, 2000; accepted for publication Jan 14, 2000.
Reprint requests: Malcolm Greaves, MD, St John's Institute of Dermatology, St John's Hospital, United Medical and Dental School, Lambeth Palace Road, London SE1 7EH, United Kingdom; fax 44 171 401 2008.

0091-6749/2000 $12.00 + 0 1/1/105706
doi:10.1067/mai.2000.105706

J ALLERGY CLIN IMMUNOL
VOLUME 105, NUMBER 4

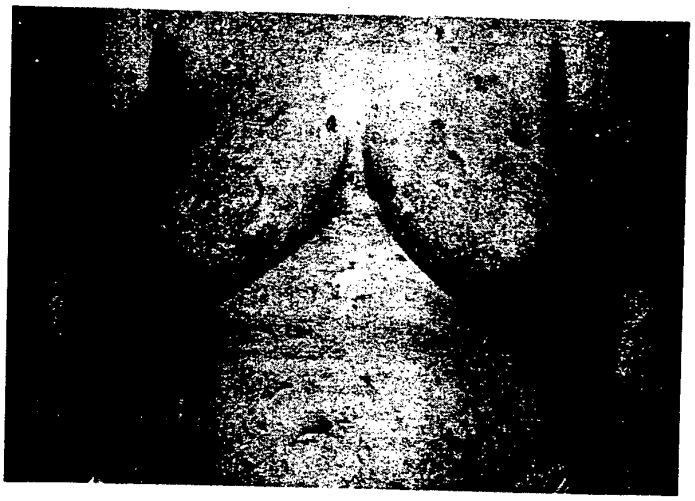


FIG 1. Chronic idiopathic urticaria.

occur in the skin, they can be extremely alarming and occasionally life threatening when they occur in the oropharynx. The swellings of angioedema are red or skin colored. Itching is less consistently associated with angioedema than with urticaria. Indeed, these swellings may not itch at all.

The classification of chronic urticaria, for the purposes of this discussion, is given in Table I.

PHYSICAL URTICARIAS

It is most important to distinguish the physical urticarias from CIU. This is because, if it turns out that a physical urticaria is the main cause of chronic urticaria in an individual, it almost invariably obviates the necessity for investigation beyond any challenge testing necessary to confirm the diagnosis. There are rare exceptions; for example, it is desirable to exclude the (rare) presence of plasma cryoproteins in patients with cold urticaria. However, it is my everyday experience that patients with physical urticarias are burdened with a costly host of unnecessary investigations and diet restrictions that shed no light whatever on the cause and do not influence the treatment of the disease.

The physical urticarias are characterized by the development of whealing and itching promptly after application of the appropriate physical stimulus. The exception is delayed pressure urticaria. A period of 2 or more hours usually elapses before whealing develops in response to applications of pressure to the skin. It is common for more than one physical urticaria to afflict a patient concurrently. For example, symptomatic dermographism and cholinergic urticaria frequently occur simultaneously. Characteristically the wheals of physical urticarias are transitory, lasting for only a few minutes or no more than an hour or 2 after removal of the provoking stimulus. Again, delayed pressure urticaria is an exception; wheals, often painful as well as itchy, last for 24 hours or more.

After whealing has been evoked and has subsided, the affected skin is frequently refractory to further provocation for a period ranging from a few hours to a day or 2 and this fact has been made use of in the management of some physical urticarias, including cold urticaria and solar urticaria.

We have published consensus guidelines for challenge testing in confirmation of the diagnosis of physical urticarias.[3] This is important because accurate characterization of a physical urticaria enables useful advice to be given to the patient regarding avoidance of symptoms, as well as for prognosis and treatment.

Only the more common physical urticarias will be detailed further here.

SYMPTOMATIC DERMOGRAPHISM (FACTITIOUS URTICARIA)

The diagnosis of symptomatic dermographism can be made by drawing the tip of a blunt-pointed instrument firmly across the skin. This causes an immediate linear red wheal that (in contrast to "ordinary" dermographism that can occur in a healthy person) manifests itching.

Any region of the body can be affected. The condition, which occurs at any age, runs on average a course of 2 to 3 years before resolving spontaneously. The wheals, which last for up to 30 minutes, fade, leaving no mark. Unlike urticaria pigmentosa caused by cutaneous mastocytosis (which also manifests dermographism—Darier's sign), there is no increase in skin mast cell numbers. Rarely, symptomatic dermographism is a sequel of scabies, lasting for several weeks after successful treatment of this infestation. There is no association with systemic disease.

The cause is unknown, but passive transfer has successfully been carried out with patient serum and nonhuman primate skin as a recipient.[4] Although conceivably IgE, the identity of the transferable factor has yet to be positively established.

TABLE I. Classification of chronic urticaria

Physical urticaria
Symptomatic dermographism
Delayed pressure urticaria
Cold urticaria
Aquagenic urticaria
Solar urticaria
Cholinergic urticaria
Vibratory angioedema
CIU
Urticarial vasculitis*

* Mentioned for the sake of completeness, but not considered in detail in this account.

With use of an in vivo dermal perfusion method we[5] established many years ago that histamine released locally is a major mediator of symptomatic dermographism. Because the condition responds well to combined H_1 and H_2 antihistamines,[6] it seems likely that dermal mast cell–derived histamine is the main, if not the only, mediator of this physical urticaria. The transitory time course of the wheals and itch would also support this notion.

DELAYED PRESSURE URTICARIA

It is not generally appreciated how common delayed pressure urticaria is. Our results show that at least 40% of all patients with CIU have concurrent delayed pressure urticaria.[7] Indeed, it is doubtful if it ever occurs in isolation. This explains the frequency of wheals at local pressure sites (waistband, palms, soles, etc) in CIU. It also explains the poor response to H_1 antihistamines in some patients with CIU because delayed pressure urticaria is generally poorly responsive to this treatment.

Characteristically the wheals of delayed pressure urticaria occur 2 to 6 hours after application of pressure to the skin and last for more than 24 hours. These wheals are itchy or quite often painful, especially on the feet. They can be disabling, especially to a manual worker, and are often associated with arthralgia. The diagnosis is made by applying a dermographometer (a spring-loaded pen-like instrument calibrated to administer a range of pressures within a continuously variable range) perpendicularly to the skin, which is examined 4 hours later. By varying the duration of application and pressure, a quantitative assessment of the severity of delayed pressure urticaria can be made.[3]

The cause of delayed pressure urticaria is unknown. The prolonged time course of the wheals distinguishes them from other categories of chronic urticaria and there is no vasculitis histologically. Our studies revealed elevated tissue levels of IL-6 but not arachidonate metabolites in lesional skin[8,9] and close similarities to late-phase reactions has been noted.[7]

The practical importance of establishing the diagnosis is evident. Apart from the predictably poor response to antihistamines and the poor prognosis (delayed pressure urticaria pursues a very long-term course), there are important management implications. If delayed pressure urticaria turns out to be an important component of the symptoms of a patient with CIU, there is little point in further autoimmune laboratory workup because delayed pressure urticaria is independent of the patient's autoantibody status (see below), and establishing an autoimmune basis for the patient's CIU is of no assistance at all in the management of the delayed pressure urticaria. Large doses of systemic steroids may be needed to control this physical urticaria in severely afflicted patients.

COLD URTICARIA

There are a number of rare subtypes of cold urticaria, but for the purposes of this account only 2 subtypes need to be considered: primary acquired cold urticaria ("essential" cold urticaria) and secondary acquired cold urticaria. Compared with most other physical urticarias, these have been intensively studied.

Primary acquired ("essential") cold urticaria

Primary acquired cold urticaria is a physical urticaria of children and young adults. Characteristically, local whealing and itching occur within a few minutes of applying a solid or fluid cold stimulus to the skin. The wheal persists for about a half hour or less before fading without a residual trace. This physical urticaria may also occur in the oropharynx (eg, after a cold drink), which may present as urticaria or angioedema. Systemic symptoms, occasionally severe and anaphylactoid, may occur after extensive exposure such as immersion in cold water.

There may be a recent history of an intercurrent virus infection *(Mycoplasma pneumoniae)*[10] and passive transfer has been successfully demonstrated to recipient human[11] and nonhuman primate[12] skin, indicating the role of a serum factor, possibly IgM or IgE.[13] Heterozygous deficiency of the protease inhibitor α_1-antichymotrypsin has been demonstrated and may be etiologically important in some patients.[14]

The dermal mast cell population density is within normal limits and there is normally no evidence of vasculitis.[15] However, repeated cold challenge at the same site can evoke evidence of structural dermal postcapillary venular damage, raising the possibility of involvement of circulating immunoreactants.[16] We and others have studied the pharmacologic mediators involved in cold urticaria by a variety of methods, including examination of venous effluent recovered from the antecubital vein of the cold-challenged forearm. Histamine has been consistently recovered, although it is probably not by itself accountable for the whealing,[15] and other mediators are implicated as well.[17-19] Exactly how dermal mast cells are triggered to release histamine and other mediators is unclear, although interesting studies by Gruber et al[20] raise the possibility of an autoimmune (possibly anti-IgE) mechanism. The prognosis is good, with spontaneous improvement occurring in an average of 2 to 3 years. Diagnosis is usually made by applying an ice cube for 5 to 15 minutes to skin and, after allowing an interval for skin rewarming, observing development of whealing.

J ALLERGY CLIN IMMUNOL
VOLUME 105, NUMBER 4

Secondary acquired cold urticaria

The diagnosis of secondary acquired cold urticaria depends on being able to demonstrate a cryoglobulin, cold agglutinin, or possibly cryofibrinogens in a patient with cold urticaria. This finding occurs in about 5% of patients with cold urticaria. The prognosis is that of the underlying disorder.

Demonstration of a cryoglobulin should prompt a search for an underlying cause, including chronic hepatitis B or C infection, lymphoreticular malignancy, or glandular fever. These considerations have been reviewed by Wanderer.[21]

The clinical picture differs from that of the "essential" type. Wheals are more persistent, may manifest purpura, and demonstrate the histologic features of vasculitis on skin biopsy specimens. The cryoglobulins may be polyclonal (post infection) or monoclonal (IgG or IgM) and complement activation may be involved.[22] A positive serologic test for syphilis has been described in cold urticaria, associated with a circulating hemolysin.[23]

CHOLINERGIC URTICARIA

In its milder presentations, cholinergic urticaria is probably the most common of all the physical urticarias. Often referred to trivially as "heat bumps," it probably occurs at some time during the lives of at least 15% of the population. It has been the subject of several useful reviews.[24,25]

Cholinergic urticaria is a physical urticaria predominantly in teenagers and younger adults and carries a good prognosis for eventual improvement, although I have had patients in whom troublesome symptoms have persisted into middle age. At least 50% of patients are also atopic. Characteristically itchy, small, red macules or papules occur on the neck, trunk, forearms, wrists, and thighs in response to heat (environmental or a hot bath or shower), exercise, or emotional stress. All these stimuli cause eccrine sweating, but the latter is not necessary as such because the rash has been described in patients with anhidrosis.[26] However, it is likely that activation of the cholinergic sympathetic innervation of sweat glands is a key mechanism. The rash can be blocked by prior atropinization of the skin.[27] The rash usually subsides within minutes if the patient "chills off." However, occasional patients in whom the rash is continuous and persistent are well recognized and represent a diagnostic trap for the unaware.[28] Severely affected patients may get associated angioedema of the skin or mucous membranes.[29] Wheezing associated with attacks of cholinergic urticaria are not uncommon even in milder cases; in more severe attacks syncope has been known to occur.[29] Cholinergic urticaria can occur without visible skin lesions (cholinergic pruritus).

The cause is unknown. A recent suggestion that some form of sweat allergy is involved[30] has not been confirmed. That a transferable serum factor may be implicated has been supported by successful transfer using serum to nonhuman primates in some cases.[31]

A small subset of patients with cholinergic urticaria will have the rash only as a consequence of food ingestion followed by exercise.[32] Some of these patients appear to have IgE-mediated allergy to certain specific food items, whereas in others the triggering factor appears to be nonspecifically related to food ingestion. The diagnosis is confirmed by exercise or hot bath challenge testing. This subject has been reviewed.[24]

We have also demonstrated reduced plasma levels of certain protease inhibitors in cholinergic urticaria.[33] That this finding is clinically significant is suggested by a placebo-controlled double-blind study that has demonstrated the ability of oral anabolic steroid treatment to both correct these lowered protease inhibitor levels and, in parallel, cause amelioration of the rash.[34] However, the routine treatment remains the use of a low-sedation H_1 antihistamine with or without an anxiolytic such as oral propranolol. Severely affected unresponsive patients may be treated cautiously with an anabolic steroid such as stanazolol. This unlicensed treatment, which is less satisfactory in women owing to the possibility of causing mild virilization, should be monitored by regular liver function tests and liver scans.

CHRONIC IDIOPATHIC URTICARIA

Clinical features

Conventionally, CIU is defined as the daily, or almost daily, occurrence of urticarial wheals for at least 6 weeks. Intermittent urticaria, although a common entity, is less well recognized. It consists of bouts of urticaria lasting days or weeks with intervals of days, weeks, or months in between. It will be considered jointly with classic CIU for the purposes of this discussion. Angioedema occurs concurrently with CIU in about 50% of cases[1] and delayed pressure urticaria in about 40%.[7]

As already discussed, care must be taken to exclude physical urticaria as the sole, or predominant, cause of the patient's disability, especially because physical urticarias frequently occur concurrently with CIU. UV is also a very important differential diagnosis (see below). CIU is common, occurring in 0.1% of the population, and 20% still have the disease after 20 years has elapsed. There is no increased frequency of atopy in CIU and the clinical features of the urticaria and angioedema are as described above (p 664). However, in comparison with physical urticarias, the individual urticarial wheals last longer—at least 8 to 12 hours. Unlike UV wheals, wheals of CIU do not cause residual pigmentation. Systemic symptoms are minimal. Patients frequently feel fatigued, especially during relapses, but respiratory, gastrointestinal, and arthralgic symptoms are rare. Angioedema may affect the oropharynx but is not life threatening. Its etiology is assumed to be the same as that for the urticaria. Gastrointestinal symptoms may occasionally accompany severe attacks. Pruritus is nearly always severe and especially troublesome in the evening and nighttime.[1]

CIU and angioedema are rare in childhood; the average duration of the disease is about 3 to 5 years in

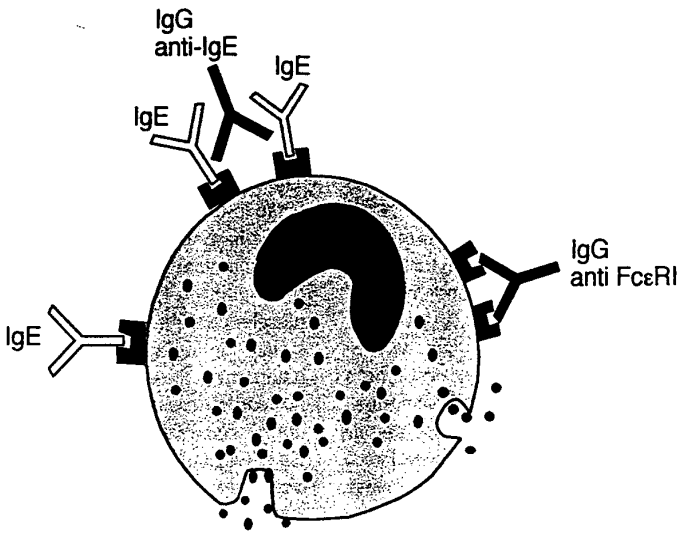


FIG 2. Functional autoantibodies of CIU. IgG-anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG-anti-FcεRI antibodies combine with and crosslink adjacent α-chains of FcεRI. Black notched membrane structures represent α-chain of FcεRI expressed on the surface of a dermal mast cell.

adults.[2] It is a cause of serious personal, social, economic, and occupational disability comparable with that associated with severe coronary heart disease.[35] Its clinical, pathologic, and etiologic features have recently been reviewed.[36]

ETIOLOGY

The target cell for CIU and angioedema is the dermal mast cell, and any hypothetic etiological mechanism should explain how this cell becomes repeatedly and extensively activated, leading to release of histamine and other mediators. No doubt other cell types are also involved, including the basophil.[37] Until recently there has been a paucity of convincing evidence-based causes. Chronic infection has frequently been cited—most recently *Helicobacter pylori*. However, recent reports have failed to confirm this association.[38,39] I have yet to see a patient in whom parasite infestation proved causative, but in regions where infestation with high loads of parasites occur, an association is possible and this needs further study. Most patients have at some time believed that food "allergy" is causative. Certainly IgE-mediated type I allergy (Gell and Coombs) caused by foods is an important cause of acute urticaria but can rarely, if ever, be substantiated as a cause of CIU. Idiosyncratic reactions to food additives are alleged to be important causes by a number of authors. However, at least in my own practice, food additives can be substantiated to be causative in no more than 5%. The gold standard must be positive placebo-controlled challenge testing.[40-42] Exclusion diets, favored by some authors, are extremely difficult to carry out satisfactorily owing to the prolonged duration of this procedure, poor patient compliance, and, invariably, ambiguous results. Aspirin does exacerbate chronic urticaria nonspecifically, as do intercurrent virus infections. However, neither are causative. Thus, until recently, the cause in the majority of patients with CIU remained enigmatic.

As early as 1962 it was reported that the absolute blood basophil count in unselected patients with CIU was significantly lower than in otherwise comparable nonurticarial controls.[43] Subsequently in 1974 I reported[44] that the basophils of unselected CIU patients released less histamine when challenged in vitro by a range of concentrations of anti-IgE than did basophils of matched nonurticarial controls. However, release evoked by nonimmunologic stimuli, which did not depend on IgE or the high-affinity IgE receptor (FcεRI), including compound 48/80, did not differ significantly between the 2 groups. These findings suggested the presence of a circulating factor causing desensitization via IgE.

In 1986 Grattan et al[45] reported the presence of a serum factor that caused whealing on autologous intradermal injection in some but not all patients with CIU. However, it was not until 1993[46] that my laboratory confirmed the identity of this factor as an IgG with specificity for the α-chain of the high-affinity IgE receptor (FcεRIα). Subsequent studies[47] demonstrated this autoantibody as a causative factor in about 25% of patients with CIU. A further 5% of patients proved to have functional anti-IgE autoantibodies[47] (Fig 2). That a subset of patients with CIU had an autoimmune basis as a result of anti-FcεRIα autoantibodies was subsequently confirmed by several authors,[48-50] the frequency ranging from 25% to 45% of the total patients with CIU. The IgG subtypes proved to be predominantly IgG1 and IgG3.[51]

J ALLERGY CLIN IMMUNOL
VOLUME 105, NUMBER 4

That CIU is, at least in some patients, autoimmune is not too surprising. An increased frequency of thyroid autoimmune disease in CIU has previously been reported by ourselves[52] and others.[53] In accordance with the proposed autoimmune basis of this subset of patients with chronic urticaria, we have also demonstrated its positive association with certain HLA-DR and -DQ alleles that are characteristically known to show increased frequency in autoimmune diseases.[54] Our own data suggest that normally IgG anti-FcεRIα autoantibodies cause direct cross-linking of adjacent receptors, thus triggering mast cell or basophil activation. However, recent work[55] raises the possibility that monovalent combination may take place, involving complement activation. This probably only occurs in instances where there is a low population density of FcεRI on the basophil or dermal mast cell membrane. The reason why little or no activation of mast cells occurs at other organ and tissue sites occurs is not clear. In vitro, lung and other noncutaneous mast cells release histamine in response to anti-FcεRIα autoantibodies.[47] However, lung mast cells are unresponsive to activated complement. Possibly, differences in interstitial fluid levels of IgG between skin and lung may also play a part.

Immunoreactive non-histamine-releasing anti-FcεRI autoantibodies have been detected in other nonurticarial autoimmune diseases, including dermatomyositis, pemphigus, and pemphigoid.[51] However, up to the present only chronic urticaria patients have been shown to manifest functional histamine-releasing anti-FcεRI autoantibodies. They do not occur in physical urticarias, atopic eczema, or other diseases in which activated mast cells have been implicated.

Of course, other circulatory factors may well also be involved, including the IgE-dependent histamine-releasing cytokine and other histamine-releasing cytokines reported by different North American groups.[56,57]

Diagnosis

Patients with autoimmune (anti-FcεRIα or anti-IgE) autoantibodies have no distinctive diagnostic clinical features. They do tend to have more severe urticaria[1] and histologic examination shows pronounced eosinophil degranulation in older lesions compared with nonautoimmune cases, but these differences are not sufficiently distinctive to use diagnostically.[58] There is no vasculitis, and direct immunofluorescence yields no specific findings. However, re-examination of the blood basophil count has revealed an extreme paucity of these cells in the peripheral blood of autoimmune compared with nonautoimmune cases, which could form the basis of a screening test.[37] Serum IgE levels are not significantly different from those of nonautoimmune patients.[1] Currently the clinical diagnosis depends on autologous serum skin testing. Maximum specificity and sensitivity is obtained if serum or plasma, obtained by venisection during a phase of disease activity, is injected, in a volume of 0.05 mL intradermally, into clinically uninvolved skin. The reaction at the injected site is examined 30 minutes later. A wheal with a diameter at least 1.5 mm greater than a control saline solution wheal is deemed positive[59] (Fig 3).

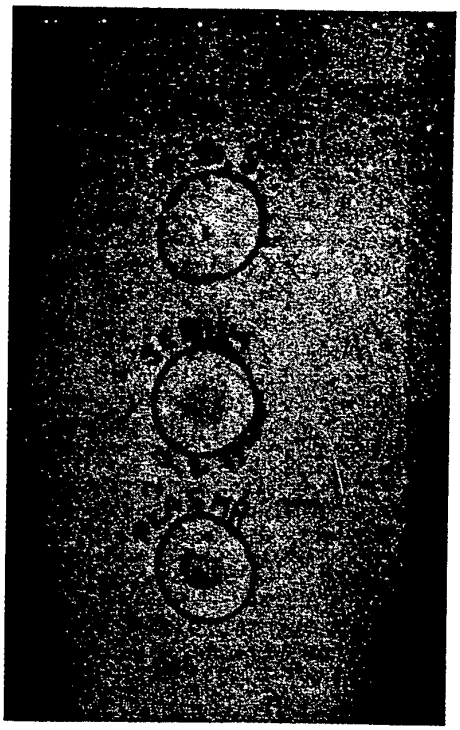


FIG 3. Autologous serum-plasma skin test. *PBS*, Saline solution negative control; serum and plasma are injected in a volume of 0.05 mL and the reaction read at 30 minutes. Both serum and plasma have given positive responses.

A positive test is suggestive but not diagnostic of an autoimmune basis for the patient's chronic urticaria. Confirmation is needed by in vitro testing of the patient's serum for anti-FcεRIα or anti-IgE autoantibodies. Regrettably, despite attempts by our own and other laboratories, no satisfactory ELISA has been developed. We rely on demonstration of histamine release from basophils of healthy low- and high-IgE donors,[47] and this remains the gold standard. However, it is time consuming and inconvenient. Western blotting is also widely used and we have shown a good concordance between results with Western blotting and with basophil histamine release using the same sera (Maurer et al, unpublished data). However, as previously indicated, false-positive results may occur in sera of patients with nonurticarial autoimmune disease because of the presence of non-histamine-releasing anti-FcεRIα immunoreactivity.

In summary, identification of disease-specific anti-FcεRIα histamine-releasing autoantibodies in 25% to 45% of CIU is clearly a useful step forward, but what about the other 50%? A few of these (no more than 5%) may have demonstrable food additive reactivity as confirmed by challenge testing (see above). Indirect evidence suggests that many of the remainder may also be autoimmune. Autoimmune and nonautoimmune cases are indistinguishable clinically and histologically. The peripheral blood basophil numbers, although almost unmeasurable in autoimmune cases, are also lower than

values in healthy controls in nonautoimmune patients. Finally, the autologous serum skin test is frequently positive although in vitro testing for histamine release from low- and high-IgE basophils turns out to be negative. Regrettably, sensitivity has had to be sacrificed in the interests of high specificity in the in vitro test.

Treatment of CIU

The routine management of autoimmune and nonautoimmune chronic urticaria is the same. General measures including avoidance of alcohol overuse, overtiredness, and overheated surroundings are important. It is also important to reassure anxious patients that the eruption is not a hallmark of cancer, HIV infection, or other underlying disease. On the other hand, elaborate and unnecessary dietary restrictions should be discouraged. Frequent tepid showers and "as-required" application of 1% menthol in aqueous cream are useful measures during relapses and well appreciated by patients.

All patients with frequent outbreaks of wheals and itching should be offered H_1 antihistamine treatment. It is important to impress on patients that regular daily dosage is essential if maximum benefit is to be achieved. Results after as-required dosage are almost always inferior and often account for alleged treatment failures. It is my practice to offer an average adult a single morning dose of a low-sedation H_1 antihistamine such as loratidine 10 mg, cetirizine 10 mg, or fexofenadine 180 mg. Cetirizine is mildly sedative. Sedation occurs with doses of loratidine above 10 mg, but I prescribe 360 mg of fexofenadine (this is twice the licensed dose) to more severely pruritic patients without risk of sedation because this antihistamine is lipophobic and does not penetrate the blood-brain barrier. However, it is important to take into account the diurnal periodicity of symptoms in each patient. There is no point in prescribing a morning dosage of an antihistamine if symptoms are restricted to evening and nighttime, as is frequently the case.[1]

In the event that pruritus at night is troublesome, I add a sedative antihistamine such as hydroxyzine 25 to 50 mg. In more severely afflicted patients the tricyclic antihistamine doxepin 25 to 50 mg is useful as a single nocturnal dose. Because anxiety and depression are a feature of patients with severe chronic urticaria and angioedema, this drug, which is also an H_2 antihistamine, a powerful sedative, an anxiolytic, and an antidepressant, is appropriate. However, doxepin is metabolized by the cytochrome P450 enzyme system and care should be taken to avoid concurrent administration of other drugs (eg, macrolide antibiotics) similarly metabolized. It is also important to warn patients who may require, for example, motor car driving skills in the morning that their cognitive function and reflex activity may be impaired for up to 24 hours after a nocturnal dose of hydroxyzine, doxepin, or similar sedative H_1 antihistamine. The role of H_2 antihistamines is controversial. We have shown in several controlled studies[6,60,61] that there is a statistically significant benefit from combination treatment with H_1 and H_2 antihistamines, but it is unclear whether this represents a significant clinical benefit. I tend to give patients the benefit of the doubt on this issue, especially if the patient happens to be troubled by gastric hyperacidity, heartburn, or dyspepsia.

The role of systemic corticosteroids is limited. I occasionally prescribe short tapering courses (eg, 30 mg of prednisolone daily reducing to zero over 10 days) in special circumstances where, for example, rapid control is needed to cover an important social or occupational event such as a wedding ceremony or an important examination. However, prolonged daily treatment nearly always leads to severe systemic toxicity accompanied by poor control of urticaria and severe rebound on attempts to withdraw.

Leukotriene antagonists have received some attention as potential nonsteroid therapies for chronic urticaria, but their role, if any, remains to be established.

What can be done for the severely affected patient recalcitrant to the above measures? If the patient turns out to be autoantibody positive, there are a number of options (see below). Autoantibody-negative patients can be considered for cyclosporine treatment. Cyclosporine is of proved value in autoantibody-positive chronic urticaria[62] but is also effective in most cases of severe autoantibody-negative disease. I use doses of 3 to 4.5 mg/kg for up to 3 months at a time. Most (>75%) show an excellent response. Of these, one third remain in remission after withdrawal, one third relapse but only mildly, and one third relapse to the extent that they were affected before cyclosporine treatment. I have only once seen what appeared to be a "rebound" relapse on withdrawal. Obviously blood pressure and renal function need to be monitored and the treatment is unsuitable for patients with risk factors related to malignant disease such as a strong family or personal history of cancer, positive cervical smear, etc.

Management of autoimmune urticaria

As previously indicated, the initial treatment is the same regardless of whether the patient has an autoimmune etiology for the disease. However, patients with autoimmune chronic urticaria tend to be more severely affected[35] and on the whole less responsive to H_1 antihistamine treatment. In these circumstances, and where the disease is clearly causing severe impairment of the patient's social, occupational, and domestic life, a number of options can be considered. Cyclosporine has already been mentioned. We have recently completed a placebo-controlled trial of oral cyclosporine in autoantibody-positive patients with chronic urticaria,[62] with impressive results. The details of the regimen for cyclosporine treatment are as for nonautoimmune patients (see above). Other options include intravenous Ig infusions[63] and plasmapheresis.[64] The reader is referred to the appropriate references for further details. However, it should be emphasized that none of these measures are curative and that they are most appropriately carried out in a specialized center.

REFERENCES

1. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FceRI or anti-IgE autoantibodies. J Am Acad Dermatol 1999;40:443-50.
2. Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angioedema—a review of 554 patients. Br J Dermatol 1969;81:588-97.
3. Black AK, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. Clin Exp Dermatol 1996;21:424-6.
4. Murphy GM, Zollman PE, Greaves MW, Winkelmann RK. Symptomatic dermographism (factitious urticaria)—passive transfer experiments from human to monkey. Br J Dermatol 1987;116:801-4.
5. Greaves MW, Sondegaard J. Urticaria pigmentosa and factitious urticaria: direct evidence for release of histamine and other smooth-muscle-contracting agents in dermographic skin. Arch Dermatol 1970;101:418-25.
6. Breathnach SM, Allen R, Milford-Ward A, Greaves MW. Symptomatic dermographism: natural history, clinical features and response to therapy. Clin Exp Dermatol 1983;8:463-76.
7. Barlow RJ, Warburton F, Watson K, Black AK, Greaves MW. The diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol 1993;24:954-8.
8. Lawlor F, Bird C, Camp RDR, Barlow R, Barr RM, Black AK, et al. Increased interleukin-6 but reduced interleukin-1 in delayed pressure urticaria. Br J Bermatol 1993;128:500-3.
9. Lawlor F, Barr RM, Black AK, Cromwell I, Isaacs J, Greaves MW. Arachidonic acid transformation is not stimulated in delayed pressure urticaria. Br J Dermatol 1989;121:317-21.
10. Neittaanmaki JJ. Cold urticaria: clinical findings in 270 patients. J Am Acad Dermatol 1985;13:636-44.
11. Houser DD, Arbesman CE, Ito K, Wicher K. Cold urticaria: immunological studies. Am J Med 1970;49:23-33.
12. Misch K, Black AK, Greaves MW, Almosawi T, Stanworth DR. Passive transfer of idopathic cold urticaria to monkeys. Acta Derm (Stockh) 1983;63:163-4.
13. Wanderer AA, Maselli R, Ellis EF, Ishizaka KJ. Immunological characterisation of serum factors responsible for cold urticaria. Allergy 1971;48:13-22.
14. Wallengren LB. Heterozygous a1-antichymotrypsin deficiency may be associated with cold urticaria. Allergy 1992;47:456-8.
15. Lawlor F, Black AK, Breathnach AS, McKee P, Sarath Chandra P, Bhogal B, et al. A timed study of the histopathology, direct immunofluorescence and ultrastructural findings in idiopathic cold contact urticaria over a 24 hour period. Clin Exp Dematol 1989;14:416-20.
16. Eady RAJ, Greaves MW. Induction of cutaneous vasculitis by repeated cold challenge in cold urticaria. Lancet 1978;1:336-7.
17. Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.
18. Keahey TM, Greaves MW. Cold urticaria: dissociation of cold-evoked histamine release and urticaria following cold challenge. Arch Dermatol 1980;116:174-7.
19. Ormerod AD, Black AK, Dawes J, Murdock RD, Koro O, Barr RM, Greaves MW. Prostaglandin D2 and histamine release unaccompanied by evidence of platelet activation. J Allergy Clin Immunol 1988;82:586-9.
20. Gruber BC, Thaeza MC, Marchase MJ, Aquello V, Kaplan AP. Autoantibodies in urticarial syndromes. J Invest Dermatol 1988;90:213-7.
21. Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis and management. J Allergy Clin Immunol 1990;85:965-81.
22. Constanzi JJ, Coltman JR, Donaldson VH. Activation of complement by a monoclonal cryoglobulin associated with cold urticaria. J Lab Clin Med 1969;74:902-10.
23. Harris KE, Lewis T, Vaughan JM. Haemoglobinuria and urticaria from cold occuring singly or in combinations: observations referring especially to the mechanism of urticaria with some remarks upon Raynaud's disease. Heart 1929;14:305-36.
24. Hirschmann JV, Lawlor F, English SJC, Lowback JB, Winkelmann RK, Greaves MW. Cholinergic urticaria. Arch Dermatol 1987;123:462-7.
25. Zuberbier T, Althaus C, Chantraine-Hess H, Czarnetski BM. Prevalence of cholinegic urticaria in young adults. J Am Acad Dermatol 1994;31:478-81.
26. Kay DM, Maibach HR. Pruritus and acquired anhidrosis: two unusual cases. Arch Dermatol 1969;100:291-3.
27. Herxheimer A. The nervous pathway mediating cholinergic urticaria. Clin Sci 1956;15:195-205.
28. Murphy GM, Black AK, Greaves MW. Persisting cholinergic erythema—a variant of cholinergic urticaria. Br J Dermatol 1983;109:343-8.
29. Lawrence CM, Jorizzo JL, Black AK, Coutts A, Greaves MW. Cholinergic urticaria with associated angioedema. Br J Dermatol 1981;105:543-50.
30. Adachi J, Aoki T, Yamatodari A. Demonstration of sweat allergy in cholinergic urticaria. J Dermatol Sci 1994;7:142-9.
31. Murphy GM, Greaves MW, Zollman P, Stanworth D. Cholinergic urticaria: passive transfer experiments from human to monkey. Dermatologica 1988;177:338-40.
32. Kivity S, Snech E, Grief J, Topilsky N, Mekori YA. The effect of food and exercise on the skin response to compound 48/80 in patients with food-associated, exercise-induced urticaria angioedema. J Allergy Clin Immunol 1988;81:1155-8.
33. Eftekhari N, Milford Ward A, Allen R, Greaves MW. Protease inhibitor profiles in urticaria and angioedema. Br J Dermatol 1980;103:33-9.
34. Wong E, Eftekhari N, Greaves MW, Milford Ward A. Beneficial effects of danazol on symptoms and laboratory changes of cholinergic urticaria. Br J Dermatol 1987;116:553-6.
35. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. Br J Dermatol 1997;136:197-201.
36. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-72.
37. Sabroe RA, Francis DM, Barr RM, Black AK, Greaves MW. Anti-FceRI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol 1998;102:651-8.
38. Schnyder B, Helbling A, Pichler WJ. Chronic idiopathic urticaria: natural course and association with Heliobacter pylori infection. Int Arch Allergy Immunol 1999;119:60-83.
39. Liutu M, Kalimo K, Uksila J, Kalimo H. Etiological aspects of chronic urticaria. Int J Dermatol 1998;37:515-9.
40. May CD. Are confusion and controversy about food hypersensitivity really necessary? J Allergy Clin Immunol 1985;75:329-33.
41. Pastorello EA. Evaluating new tests for the diagnosis of food allergy. Allergy 1995;50:289-91.
42. Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria including the physical urticarias. Br J Dermatol 1975;93:135-144.
43. Rorsman H. Basopenia in urticaria. Acta Allergol 1962;17:168-84.
44. Greaves MW, Plummer VM, McLaughlan P, Stanworth DR. Serum and cell-bound IgE in chronic urticaria. Clin Allergy 1974;4:265-71.
45. Grattan CEH, Wallington TB, Warin RP. A serological mediator in chronic idiopathic urticaria: a clinical immunological and histological evaluation. Br J Dermatol 1986;114:583-90.
46. Hide M, Francis DM, Grattan CEH, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. N Engl J Med 1993;328:1599-604.
47. Niimi N, Francis DM, Kermani F, Greaves MW, Black AK, O'Donnell BF, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106:1001-6.
48. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschlager M, et al. Serum IgG autoantibodies directed against the a-chain of FceRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606-12.
49. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996;98:89-98.
50. Tong LJ, Balakrishnan G, Kochan JP, Kinet J-P, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997;99:461-5.
51. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FceRI autoantibodies in autoimmune-mediated disorder: identification of a structure-function relationship. J Clin Invest 1998;101:243-51.
52. O'Donnell BF, Black AK, Greaves MW. Organ- and non-organ-specific autoimmunity in chronic urticaria [abstract] Br J Dermatol 1995;133(145 Suppl):42.
53. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity—a study of 90 patients. J Allergy Clin Immunol 1989;84:66-71.

54. O'Donnell BF, O'Neill CM, Francis DM, Niimi N, Barr RM, Barlow RJ, et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br J Dermatol 1999;140:853-8.
55. Ferrer M, Nazakawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol 1999;104:169-72.
56. Claveau J, Lavoie A, Brunet C, Bedford PM, Hiber J. Chronic idiopathic urticaria: possible contribution of histamine releasing factor to the pathogenesis. J Allergy Clin Immunol 1993;92:132-7.
57. MacDonald SM, Rafnar T, Langdon J, Lichtenstein LM. Molecular identification of an IgE-dependent histamine releasing factor. Science 1995;269:688-90.
58. Sabroe RA, Poon E, Orchard GE, Lane D, Francis DM, Barr RM, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FceRIa or anti-IgE autoantibodies. J Allergy Clin Immunol 1999;103:484-93.
59. Sabroe RA, Grattan CEH, Francis DM, Barr RM, Black AK, Greaves MW. The autologous serum sin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999;140:446-52.
60. Commens CA, Greaves MW, Cimitidine in chronic idiopathicurticaria: a randomised double-blind study. Br J Dermatol 1978;99:675-6.
61. Thomas SE, Glenny H, Bleehen SS, Grewel MW, Pilgrim J, Rowell N, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomised double-blind study. Br J Dermatol 1987;117:81-8.
62. Grattan CEH, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomised double-blind study of cyclosporin in chronic idiopathic urticaria. Br J Dermatol 1999. In press.
63. Grattan CEH, Francis DM, Slater NGP, Barlow RJ, Greaves MW. Plasmapheresis for severe unremitting chronic urticaria. Lancet 1992;339:1078-80.
64. O'Donnell BF, Barr RM, Blac AK, Francis DM, Greaves MW. Intravenous immunoglobulin in chronic autoimmune urticaria. Br J Dermatol 1998;138:101-6.

PRESENTED AT THE ROUNDTABLE, "CURRENT MANAGEMENT OF URTICARIA AND ANGIOEDEMA," SUPPORTED BY AN EDUCATIONAL GRANT FROM MARION MERRELL DOW INC.

Urticaria and angioedema: Diagnosis and evaluation

Kevin D. Cooper, MD, *Ann Arbor, Michigan*

Because urticaria clears spontaneously in most patients, an extensive workup is not advised during the early weeks of an urticarial eruption. Whether and when to perform a screening workup or a more extensive workup depend on the degree of suspicion that the patient is ill, the urgency with which the patient presses for an answer, and the presence or absence of signs or symptoms that might lead the physician to pursue a diagnosis other than chronic idiopathic urticaria. Angioedema may occur with urticaria, and when it does, the prognosis is worse. Whereas urticaria manifests as circumscribed edema involving the superficial dermis, angioedema involves primarily the deep dermis or subcutaneous or deeper layers. Individual urticarial lesions usually disappear within 2 to 4 hours, whereas those of angioedema can persist for 72 hours. The workup for patients with chronic angioedema can be similar to that for patients with urticaria. However, several additional diagnostic possibilities should be pursued in patients with angioedema, such as hereditary angioedema caused by C1-esterase inhibitor deficiency, because anabolic steroids are effective in the treatment of these conditions. (J AM ACAD DERMATOL 1991;25:166-76.)

Urticaria and angioedema, both common disorders, can be frustrating for patient and physician alike. Surveys show that approximately 0.1% of the population has urticaria on physical examination[1] and that cumulative prevalence rates are in the 15% to 25% range.[2,3] Therapy is often less than optimal, and the patient, physician, or both may believe that if the underlying cause could be unearthed, treatment would be more satisfactory. At the same time, both may be concerned that the urticaria or angioedema is a manifestation of an associated underlying illness.

Since urticaria clears spontaneously within a few months in most patients, it is not prudent to begin an extensive workup during the early weeks of an urticarial eruption. For this reason, investigators have divided urticaria into acute and chronic, with chronic urticaria defined as urticaria that recurs in episodes of more than 6 weeks' duration.

Among patients seeking help from a family practice group, 30% had chronic urticaria.[4] Acute urticaria occurs more commonly in young adults and children, and by definition, it is a self-limited disorder. Chronic urticaria is more common in middle-aged women.[3,4] Among patients with urticaria alone, 50% continued to have lesions 1 year after the initial visit to a dermatology clinic, and 20% continued to experience episodes for more than 20 years.

Urticaria often occurs with angioedema. When it does, the prognosis is worse, with 75% of patients suffering from recurrent episodes for more than 5 years.[5,6] In children as in adults, urticaria can persist for a protracted period. In a study of pediatric patients with chronic urticaria who were fol-

Table I. Differential diagnosis of urticaria

Insect bites (papular urticaria)
Erythema multiforme
Bullous pemphigoid (urticarial stage)
Urticaria pigmentosa
Vasculitis and polyarteritis
Lupus erythematosus
Morbilliform drug eruptions
Dermatitis herpetiformis (early lesion)*
Follicular mucinosis*
Amyloidosis*
Myxedema*
Cutaneous larva migrans*
Strongyloidiasis*
Benign neoplasias*

*These conditions are included in this table for completeness; they are only rarely confused with urticaria.

From the Immunodermatology Unit, Department of Dermatology, University of Michigan Medical Center.

Reprint requests: Kevin D. Cooper, MD, Associate Professor and Director, Immunodermatology Unit, Department of Dermatology, University of Michigan Medical Center, R5548 Kresge I, Box 0530, Ann Arbor, MI 48109.

16/0/29711

Volume 25
Number 1, Part 2
July 1991

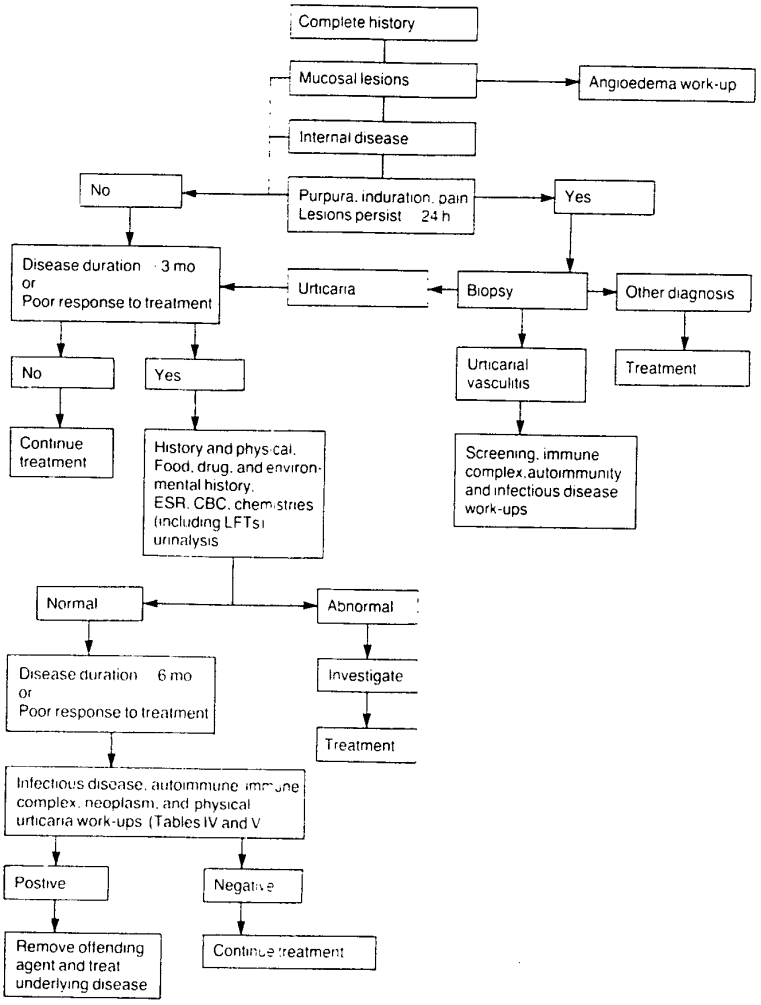


Fig. 1. This algorithm describes an approach to the workup of urticaria. *LFTs*, Liver function tests. (Modified from Cooper KD. A practical workup for urticaria. Clin Cases Dermatol [not published].)

lowed for 2 years, 42% continued to have active urticaria.[7]

It would seem that a search for an underlying cause would be worthwhile for all patients with chronic urticaria or angioedema. However, it is even more difficult to determine the cause of chronic urticaria than that of acute urticaria.[5] Although some studies have determined the cause of chronic urticaria in as many as 15% to 25% of cases,[5, 7, 8] most practitioners identify a cause in less than 10% of their patients.

This article examines the workup of patients with urticaria and angioedema and specifically addresses the question, "How far do you go?" Tables I and II outline a differential diagnosis for urticaria and angioedema; Fig. 1 and 2 and Tables III through V offer algorithms and some general guidelines for proceeding in the workup of patients with urticaria or angioedema. However, the question of whether to perform a screening workup or a more extensive one depends on many variables. These factors include the degree of suspicion that the patient is ill, the urgency with which the patient presses the physician for an answer, and the presence or absence of signs or symptoms that might lead the physician to pursue an investigation in one or several of the categories presented.

DIFFERENTIAL DIAGNOSIS

Urticaria manifests as circumscribed edema involving the superficial portion of the dermis. It is almost always associated with intense pruritus. Le-

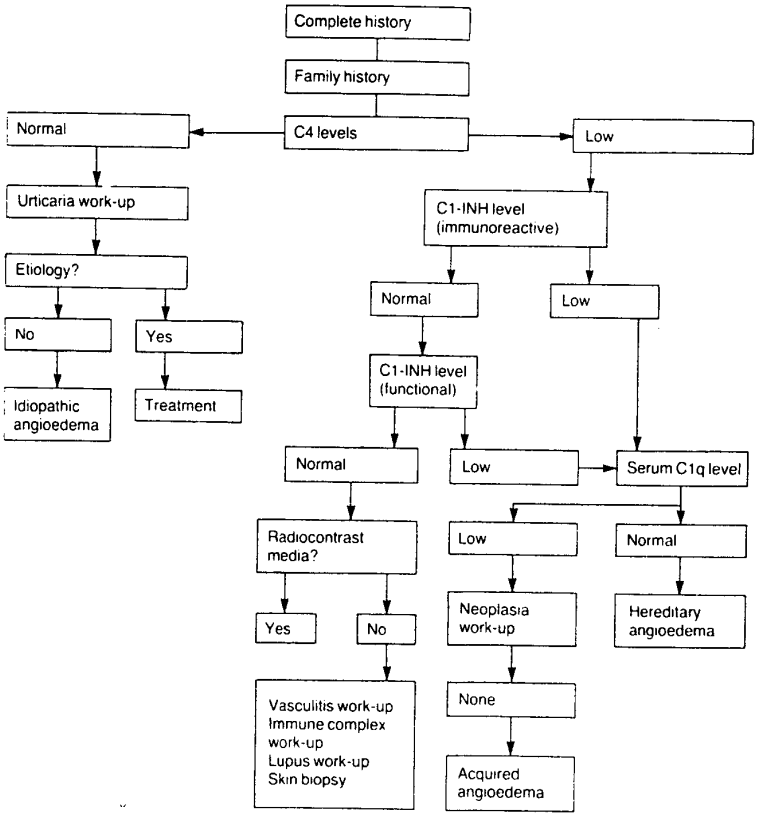


Fig. 2. This algorithm describes an approach to the workup of angioedema. C1-*INH*, C-1 esterase inhibiter. (Modified from Cooper KD. A practical workup for angioedema. Clin Cases Dermatol [not published].)

Table II. Differential diagnosis of angioedema

Anaphylaxis
Melkersson-Rosenthal syndrome
Erysipelas
Cellulitis
Contact dermatitis
Photodermatitis
Lymphedema*
Congestive heart failure*
Other deep edematous or diffusely infiltrating conditions

*These conditions are included in this table for completeness; they are only rarely confused with angioedema.

sions are raised and erythematous and may be isolated from each other or confluent. They may have edematous, pale centers (wheal), and surrounding erythema (flare). Annular, configurate patterns can be observed.

Angioedema is distinguished from urticaria by the edematous process that involves primarily the deep dermis or subcutaneous or deeper layers. Angioedema may be more painful than pruritic. The most frequently involved sites of angioedema include the face (especially the lips and periorbital area), tongue, pharynx, hands, feet, penis, and scrotum. Whereas individual urticarial lesions usually disappear within 2 to 4 hours, lesions of angioedema can persist for as long as 72 hours. Both urticarial and angiodematous lesions can arise quickly.

Although hereditary angioedema can cause true pharyngeal edema and fatal asphyxiation, chronic idiopathic angioedema or acquired angioedema is rarely, if ever, associated with laryngeal edema. They can, however, cause enough pharyngeal edema to cause hoarseness and difficulty in swallowing food. These complications must be distinguished from the difficulty in initiating speech and respiratory stridor associated with laryngeal involvement, because these symptoms may be early signs of

Volume 25
Number 1, Part 2
July 1991

Table III. Extended urticaria workup when external agents are suspected

Foods	Drugs	Environmental agents
Detailed history RAST or skin tests Elimination diet (water, rice, lamb) Food challenges Tartrazine and ASA	Antibiotics Anesthesia Blood products Serum products Other drugs	Contactants (history and challenge) Inhalants (history, associated respiratory symptoms?) RAST or skin tests

ASA, Acetylsalicylic acid.

Table IV. Extended urticaria workup when other diseases are suspected

Infectious diseases	Autoimmune	Immune complexes	Neoplasms (rare)
Upper respiratory Pharyngeal cultures ASO + streptozyme Sinus + dental films	Antinuclear antibody	C3, C4, CH50	Chest X-ray film CT scans
Syphilis VDRL	Extractable nuclear antigen	Raji cell assay	Serum protein electrophoresis
Parasites EOS Stools for ova and parasites	Rheumatoid factor	Clq binding assay	
Candida Vaginal smear Candidin skin test	Thyroid microsomal Ab	Cryoglobulins Cryofibrinogens Cold hemolysins	
Viral HBsAg + Ab Monospot HIV			

ASO, Antistreptolysin O; *VDRL*, Venereal Disease Research Laboratories; *EOS*, eosinophils; *HBsAg*, hepatitis B surface antigen.

potentially life-threatening airway compromise.[9] Another severe complication of angioedema may be involvement of the lower gastrointestinal tract with symptoms of an acute abdomen.

Differential diagnosis of urticaria. Although identifying an eruption as urticaria is usually not difficult, some conditions can be morphologically similar enough to urticaria to cause confusion (Table I). Papular urticaria appears as small grouped papules. They usually result from hypersensitivity to insect bites and as such are generally located on the lower parts of the legs. Individual lesions last longer than those of urticaria because patients have both an immediate and a delayed reaction to the bite.

Erythema multiforme can be urticarial in appearance; one series documented it as the entity most commonly misdiagnosed as urticaria.[4] Typical cases of erythema multiforme are more acrally distributed than urticaria, and classic cases have target (iris) lesions. Lesions of erythema multiforme persist longer than the 3 to 4 hours typical of most types of urticaria, and a skin biopsy is usually diagnostic.

Bullous pemphigoid can exist as an urticarial plaque, which may or may not form a blister. A routine skin biopsy specimen may not distinguish the two if a mild, mixed-cell infiltrate is the only abnormality. In this situation a skin biopsy of perilesional skin for immunofluorescence microscopic examination is the diagnostic procedure of choice and will reveal in vivo–bound autoantibodies along the dermoepidermal junction.

Lesions of urticaria pigmentosa will urticate when the site is scratched (Darier's sign). However, the condition is distinguishable from urticaria, because the individual lesions of urticaria pigmentosa are papular and hyperpigmented when not urticated.

Table V. Extended urticaria workup when physical urticarias are suspected

Type of urticaria	Test
Dermographism	Stroke back
Cold	Ice cube
Cholinergic	Exercise, methacholine
Delayed pressure	Sand bag (wait >3 hr)
Solar	Phototest
Aquagenic	Water compresses
Vibratory angioedema	Vibratory mixer

Diagnosis is confirmed when the skin biopsy results show an abnormal increase in the collections of mast cells in the dermis.

In addition to occurring with vasculitides and lupus erythematosus, urticaria may be mimicked by individual lesions of vasculitis, polyarteritis nodosa, and subacute cutaneous lupus erythematosus. Morbilliform drug eruptions may also appear to be urticarial. These and the other conditions listed in Table I can be distinguished from urticaria through clinical and histologic testing.

Differential diagnosis of angioedema. Typical cases of angioedema are easily diagnosed. Acute swelling of deep tissues must be distinguished from anaphylaxis and the possibility of airway obstruction considered. Whereas lesions of angioedema typically clear within 48 to 96 hours, those of the other conditions listed in Table II are more persistent. Swollen tongue and lips with seventh nerve palsy are characteristic of Melkersson-Rosenthal syndrome. The lesions of erysipelas and cellulitis are generally more superficial, hot, and tender than those of angioedema. Contact dermatitis and photodermatitis of the face or eyelids are usually accompanied by epidermal changes such as scaling, thickening, or weeping. Other forms of deep edema must occasionally be considered.

WORKUP OF URTICARIA

The algorithm in Fig. 1 is designed to help determine whether to order diagnostic tests, and if so, which ones. There is a considerable difference of opinion regarding the extent of laboratory workups in urticaria, and thus this algorithm should be considered a rough guideline to be tailored to the varied situations faced by practitioners and their patients. The patient should have a realistic expectation that the workup may be unproductive but will serve to rule out serious underlying disease.

Physicians should at least take a directed medical history and conduct a physical examination for all patients. They should ask patients specifically whether they have an opinion about what is triggering their urticaria. The medical history should be directed toward sinusitis, arthritis or arthralgias, urinary symptoms, and constitutional symptoms such as weight loss, fever, and malaise. Recent infections of the upper respiratory tract, especially in children, are the most common urticaria-triggering infections.[4, 7, 10] A directed physical examination may include examination of the skin, ears and throat, lymph nodes, lungs, and joints. If abnormalities are detected, a detailed laboratory or radiographic workup is indicated to determine whether a treatable underlying disease is involved.

The external causative agents listed in Table III should be surveyed. Specifically, physicians should inquire about foods most commonly associated with urticaria, such as fish, shellfish, eggs, nuts, and strawberries. Food-induced urticaria occurs most commonly as an acute urticaria, and a dietary log can be used if foods are suspected. Patients may be warned at this time that aspirin and related salicylates can exacerbate urticaria in 40% of people with urticaria,[11] and they should be questioned about aspirin ingestion as well as ingestion of other analgesics, penicillin,[4] sulfonamides, and thiazides. An elimination diet or challenge should not be attempted at this point unless the history is suggestive.

Intracutaneous scratch or prick testing can also be used to determine if a patient has an allergic risk to certain suspected foods. If results of intracutaneous testing are negative, it is unlikely that the suspected food is the culprit. Because multiple positive tests are common, a positive test only confirms allergic risk and does not imply that the food is an offending agent. Radioallergosorbent (RAST) testing for serum IgE antibodies to foods is similar in its high sensitivity and low specificity.

A recent history of insect stings or exposure to blood products, anesthesia, or radiocontrast media may be significant. Patients usually are aware of agents that induce contact urticaria, such as raw meat, fish, or vegetables, animal dander, or other mast cell degranulators. Some patients can correlate outbreaks of urticaria with exacerbations of allergic rhinitis or asthma; they may be candidates for skin testing, allergen avoidance, and desensitization.

If no abnormality or historic information is identified to suggest a likely cause of the urticaria, the

next step hinges on the duration of individual urticarial lesions. Individual lesions of urticaria typically last less than 6 hours, whereas deep lesions of angioedema or delayed pressure urticaria persist longer.

Superficial urticarial lesions lasting longer than 6 to 24 hours have been associated with urticarial vasculitis, and a biopsy sample should be taken. A histologic diagnosis of vasculitis in an urticarial lesion has been associated with concurrent arthralgia or arthritis, palpable purpura, nephritis, neuritis, and more frank lesions of cutaneous or systemic vasculitis.[12-14] Direct immunofluorescence can reveal immune complex deposition and fibrin in the vessel walls, and there may be hypocomplementemia consistent with an immune complex deposition disorder.[15] Although at least some patients with urticarial vasculitis and hypocomplementemia represent a subset of patients with lupus erythematosus, a positive biopsy specimen should trigger screening workups for immune complexes, autoimmunity and infectious diseases (Table IV).

Care should be taken not to confuse true urticarial vasculitis with neutrophilic urticaria. Although both are histologically characterized by neutrophils in the walls of swollen dermal blood vessels, neutrophilic urticaria lacks the leukocytoclasia, fibrinoid deposition, and hemorrhage seen in urticarial vasculitis. In a recent study,[16] direct immunofluorescence results were normal in patients with neutrophilic urticaria, and patients lacked the systemic complaints described above as well as evidence of hypocomplementemia and connective tissue disease. The long duration of the lesions (up to 72 hours) and high frequency of dermographism and physical urticarias[17] suggest that neutrophilic urticaria may be a separate form of urticaria, although in some cases the neutrophil-rich infiltrate may represent a stage of evolution of lesions of typical urticaria.

If a skin biopsy sample taken from a patient with lesions lasting more than 2 to 4 hours does not reveal urticarial vasculitis, it may reveal another process distinct from urticaria, such as erythema multiforme. More commonly, biopsy findings characteristic of urticaria, such as a mixed-cell infiltrate, an eosinophil-rich infiltrate, or an infiltrate dominated by mononuclear cells, may be seen.[18-20] Such findings in conjunction with lesions lasting more than 3 hours indicate that it is probably worthwhile to investigate for evidence of physical urticarias (Table V), particularly dermographism, cold urticaria, and delayed pressure urticaria.

Patients in whom the medical history and physical examination are normal and whose lesions are of short duration, or patients with lesions of long duration and biopsy evidence of typical urticaria (in whom physical urticarias have been excluded) should be treated empirically with antihistamines. If by the end of 6 weeks the urticaria has not cleared, a screening workup may be indicated. Further workup can also be initiated if the patient responds poorly to a variety of therapeutic regimens and displays anxiety about an underlying process.

The screening workup should include a complete history and physical examination if they were not performed earlier. They should be directed as previously described. At this point laboratory evaluation can include an erythrocyte sedimentation rate to screen for an active inflammatory or neoplastic process and a complete blood count with differential. Some examples of abnormalities relevant to urticaria include the following: (1) A high white blood cell count with neutrophilia might indicate bacterial or fungal infection. (2) Eosinophilia might indicate helminthic disease, atopy, drug eruption, or a peculiar syndrome associated with recurrent attacks of urticaria and/or angioedema, fever, and massive weight gain.[21] (3) Atypical leukocyte morphologic findings may indicate a myelodysplasia or a hematologic malignancy. Anemia may indicate an underlying malignancy or an autoimmune connective tissue disorder.

In an urticaria workup, liver and renal function tests are the most useful laboratory tests. Urticaria is frequently present in the early phase of hepatitis B and infectious mononucleosis, both of which may be suggested by abnormal liver function tests. Renal function tests and urinalysis may indicate nephritis or infection.

If the results of a screening workup are negative, the patient and physician are given a measure of reassurance, and empiric therapy can be continued. After 3 to 6 months, the urticaria will have stopped in most patients, but a subgroup will have persistent bouts that may or may not be well controlled medically.

The question of foods, drugs, or environmental agents can be addressed in more detail at this juncture (Table III). An elimination diet of water, rice, and lamb (or chicken) may be tried for a few weeks to decide whether the frequency of episodes can be

reduced. Suspect foods can be carefully added into the daily diet one food at a time every 2 to 3 days.

When the results of a screening workup are inconclusive, the possibility of a physical urticaria should be considered as previously indicated. Because this type of investigation can be complex and time-consuming, information from the patient's history should be used as guidelines. A wheal-and-flare response to a 3- to 5-minute challenge with an ice cube on the forearm may suggest abnormalities of serum proteins and necessitate tests for cryoglobulins, rheumatoid factors, cold agglutinins (especially mononucleosis), cryofibrinogen, antinuclear antibodies, and serum protein electrophoresis.[22] The family history is important because cold urticaria can occur as an autosomal-dominant inherited disease.[23]

Cholinergic urticaria is also a relatively common form of physical urticaria. Small pruritic truncal wheals and prominent flares occur after exercise, sweating, or hot showers. The proposed mechanism is that mast cells degranulate on liberation of acetylcholine by parasympathetic innervation at the neuromuscular junction and sympathetic innervation of sweat glands. Diagnosis is best made by having the patient exercise in the medical office (or run up and down a stairwell) until a sweat is produced and the characteristic lesions are visible. An intradermal skin test with methacholine (0.01 mg in 0.05 ml saline solution) will cause wheals and flares surrounding the injection site,[24] but test results are positive in only one third to one half of patients with cholinergic urticaria.[9] Various procedures are available for the diagnosis of the other physical urticarias (Table V).[5, 23]

A variant to be distinguished from cholinergic urticaria is adrenergic urticaria.[25] Patients with stress-related urticaria and with a methacholine skin test negative for cholinergic urticaria can be tested by an intradermal skin test with noradrenaline (3 to 10 ng in 0.02 ml of normal saline solution).

If the above tests are inconclusive, an extended workup can be performed (Tables III through V and Figs. 1 and 2). Every test in each category need not be applied to every patient. However, certain items in each category should be chosen to rule out infectious diseases (some of which may be occult), autoimmune diseases, immune complex formation syndromes, and neoplastic disorders. Among the infectious diseases, occult streptococcal pharyngitis, dental caries, sinusitis, and candidiasis may cause or exacerbate urticaria. The specific tests listed can be performed, and some physicians treat empirically with antibacterial and anticandidal antibiotics. Although the role of occult bacterial infections in causing urticaria is controversial, it is clear that helminthic and viral infections can be associated with the development of urticaria.

Several autoimmune diseases have been reported in association with urticaria. For instance, a test result positive for antinuclear antibodies suggests lupus erythematosus and necessitates more specific tests for this disorder. Findings positive for extractable nuclear antigen may indicate Ro and La autoantibodies associated with Sjögren's syndrome, subacute cutaneous lupus erythematosus, or mixed connective tissue disease. A positive rheumatoid factor might represent an immune complex depositing in dermal vessels and triggering urticaria or angioedema. Because other autoimmune tissue disorders, particularly autoimmune thyroiditis, have been associated with urticaria, a test for thyroid microsomal antibody may be useful in suspected cases. Autoantibodies to smooth muscle, parietal cells, or mitochondria can be obtained. A prolonged partial thromboplastin time may indicate a lupus anticoagulant.

A closely related group of tests is designed to detect large immune complexes or other complexed proteins (cryofibrinogens, fibrin split products) or cells (cold hemolysins). Low complement levels suggest either an autoimmune syndrome with complement deficiency or fixation of complement by circulating immune complexes. Their direct demonstration by the Raji cell or C1q binding assay (or similar assays) should trigger a workup of immune complex formation syndromes.

Urticaria is rarely the presenting sign of neoplasia. However, it can occur with neoplasms, particularly lymphomas, and carcinomas. A stool guaiac test for occult blood is economical and sensitive. Abnormal findings on a chest radiograph or a computed tomographic scan of the chest and abdomen may reveal otherwise undetectable central adenopathy or parenchymatous involvement in patients in whom a full neoplastic workup has been launched.

WORKUP OF ANGIOEDEMA

The workup for a patient with chronic angioedema can be similar to that conducted for a patient with urticaria. However, several additional diagnostic possibilities are raised and should be pursued in

Volume 25
Number 1, Part 2
July 1991

each patient because anabolic steroids are an effective treatment for hereditary angioedema caused by C1-esterase inhibitor deficiency.

Fig. 2 is an algorithm for proceeding with this workup. Again the first step is a careful history with special attention to family history and a physical examination. If the serum C4 level is normal, one can follow the path of the urticaria algorithm in Fig. 1. If the serum C4 value is low, an immunoassay test should be done to detect the amount of C1-esterase inhibitor protein. If the amount of protein is normal and yet the level of C4 is low, a functional test of C1-esterase inhibitor should be obtained, since a subgroup of hereditary angioedema produces normal amounts of a dysfunctional protein. If a normal value is found again, the patient does not have hereditary angioedema.

A low C2 or C4 level along with normal C1-estarase inhibitor levels can result from exposure to radiocontrast media, as well as from immune complex formation syndromes. A skin biopsy sample will rule out vasculitis in these situations, and the workups (Table IV) for infectious disease, autoimmunity, and immune complex disorders (including a C3 level) should be initiated to diagnose hypocomplementemic angioedema.

If the results of either the functional or immunologic assays indicate low levels of C1-esterase inhibitor, the serum C1q level should be measured to distinguish treatable hereditary angioedema from the rare association of acquired angioedema with neoplasias such as B-cell lymphoma.

A low C1q level can be from a paraneoplastic syndrome that consumes C1q and thereby secondarily depletes C1q-esterase inhibitor.[26, 27] Thus a low C1q level should trigger a workup for neoplasia (Table IV).

The diagnosis of hereditary angioedema can be made if the C1q level is normal and the levels of C2 and/or C4 and C1-esterase inhibitor are reduced.[23] This is an important diagnosis to make, because the disease is life-threatening and responds well to anabolic steroids such as danazol.[28] One should also be alert to the coexistence of lupus in patients with hereditary angioedema.[27]

REFERENCES

1. Hellgren L. The prevalence of urticaria in the total population. Acta Allergol 1972;27:236-40.
2. Nizami RM, Baboo MT. Office management of patients with urticaria: an analysis of 215 patients. Ann Allergy 1974;33:78-85.
3. Monroe EW, Jones HE. Urticaria: an updated review. Arch Dermatol 1977;113:80-90.
4. Margolis CF, Nisi R. Urticaria in a family practice. J Fam Pract 1985;20:57-64.
5. Champion RH. Urticaria. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, eds. Textbook of dermatology. Oxford: Blackwell Scientific Publications, 1986:1099-108.
6. Champion RH, Roberts SO, Carpenter RC. Urticaria and angioedema: a review of 554 patients. Br J Dermatol 1969;81:588-97.
7. Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. Ann Allergy 1983; 51:161-5.
8. Green GR, Koelsche GA, Kierland RR. Etiology and pathogenesis of chronic urticaria. Ann Allergy 1965;23:30-6.
9. Kaplan AP. Rheumatologic and immunologic diseases. In: Provost TT, Farmer ER, eds. Current therapy in dermatology. Philadelphia: BC Decker, 1986:124-31.
10. Fineman S, Ghory JE. The hospitalized child with urticaria. J Asthma Res 1976;14:27-32.
11. Matthews KP. Urticaria and angioedema. J Allergy Clin Immunol 1983;72:1-14.
12. Soter NA, Austen KF, Gigli I. Urticaria and arthralgias as manifestations of necrotizing angiitis (vasculitis). J Invest Dermatol 1974;63:485-91.
13. Soter NA. Chronic urticaria as a manifestation of necrotizing venulitis. N Engl J Med 1977;296:1440-42.
14. Sanchez NP, Winkelmann RK, Schroeter AL, Dicken CH. The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. J AM ACAD DERMATOL 1982;7:599-605.
15. McDuffie FC, Sams W Jr, Maldonado JE, Andreini PH, Conn DL, Samayoa EA. Hypocomplementemia with cutaneous vasculitis and arthritis: possible immune complex syndrome. Mayo Clin Proc 1973;48:340-8.
16. Winkelmann RK, Wilson-Jones E, Smith NP, English JSC, Greaves MW. Neutrophilic urticaria. Acta Derm Venereol (Stockh) 1988;68:129-33.
17. Peters MS, Winkelmann RK. Neurophilic urticaria. Br J Dermatol 1985;113:25-30.
18. Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. J Allergy Clin Immunol 1986;78:914-8.
19. Natbony SF, Phillips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. J Allergy Clin Immunol 1983;71:177-83.
20. Mekori YA, Giorno RC, Anderson P, Kohler PF. Lymphocyte subpopulations in the skin of patients with chronic urticaria. J Allergy Clin Immunol 1983;72:681-4.
21. Gleich GJ, Schroeter AL, Marcoux JP, Sacks MI, O'Connell EJ, Kohler PF. Episodic angioedema associated with eosinophilia. N Engl J Med 1984;310-1621-6.
22. Neittaanmaki H. Cold urticaria: clinical findings in 220 patients. J AM ACAD DERMATOL 1985;13:636-44.
23. Soter NA, Wasserman SI. IgE-dependent urticaria and angioedema. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds. Dermatology in general medicine. New York: McGraw-Hill, Inc, 1971:1282-93.
24. Fineman SM. Urticaria and angioedema. Prim Care 1987;14:503-12.
25. Shelley WB, Shelley ED. Adrenergic urticaria: a new form of stress-induced hives. Lancet 1985;2:1031-3.
26. Gelfand JA, Boss GR, Conley CC, Reinhart R, Frank

MM. Acquired C1-esterase inhibitor deficiency in angioedema: a review. Medicine (Baltimore) 1979;58: 321-8.
27. Donaldson VH, Hess EV, McAdams AJ. Lupus-erythematous-like disease in three unrelated women with hereditary angioneurotic edema. Ann Intern Med 1977;86:312-3.
28. Gelfand JA, Shermis RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. N Engl J Med 1976;2195:1444-8.

COMMENTARY AND DISCUSSION

Workup of patients with urticaria and angioedema

Food testing and skin testing

Dr. Cooper. I hardly ever use elimination diets, but I think if patients keep a dietary log or the history is suggestive, an elimination diet is an option. Food challenges can also be done, or you might want to test for tartrazine and aspirin. I do not do specific tartrazine testing; I just have people avoid them.

Dr. Schwartz. I believe that if there is a reasonable history to make you suspect food allergy, you would want to skin test the patient before trying food challenges.

Dr. Cooper. Skin testing is very simple, and a negative reaction with intractuaneous skin testing probably rules out IgE-dependent food sensitivity.

Dr. Greaves. We should make it clear that we are now talking about patients with an acute urticaria. If a person goes to the seaside, eats some shellfish, and has urticarial whealing, I believe that skin tests would confirm that diagnosis. However, I do not think skin testing is useful in patients with chronic urticaria who may or may not have some vague reaction to food. I think this is where the dermatologists and allergists differ. My view is that skin testing is not a productive procedure in patients with chronic urticaria. Acute urticaria is a different matter; skin testing can be very discriminatory in patients with acute attacks.

Dr. Schwartz. I am not sure that I have ever skin tested a patient with urticaria because I have never been convinced by history that there is any reason to test for food. If a patient has a reaction within 2 hours each time they eat a certain food, that would be a history of food-induced urticaria. However, if the patient has the reaction only occasionally and most of the time they do not have it, then that is not a history of food-induced urticaria. Also, if the reaction happens the day after the patient eats that food, that is not a positive history, and that is usually the case, that the reaction is just coincidence.

If the history is unclear, I still believe that I would do a skin test before I would do food challenges, because this may narrow the number of different foods to be tested. You can challenge with perhaps only two foods a day. It is a time-consuming procedure. However, skin testing is fairly simple, and if the test result is negative, you do not need to proceed with food challenges. If the test result is positive, then you can consider the food challenges. The bottom line is that I certainly would not recommend food testing as a routine procedure.

Dr. Soter. In the New York area at least, food testing is probably overused. I see many patients who spend hundred of dollars on negative skin test results.

Dr. Greaves. I think we have to emphasize to physicians who might read this that skin testing is *not* a useful, routine procedure in chronic urticaria.

Dr. Schwartz. Clearly it should not be routine.

Dr. Ellis. I think we agree that foods are unlikely to be a major issue in patients with chronic urticaria.

Aeroallergens and urticaria

Dr. Schwartz. I am not certain what we should recommend about skin testing in association with aeroallergens and urticaria. Yes, hives can occur if you apply allergens to the skin. Certainly somebody who has IgE antibodies to dust allergens and who lies down in a bed of dust is likely to have hives. However, a lot of people with hay fever and atopic respiratory conditions will have positive skin test results that may not have anything to do with urticaria.

Dr. Greaves. I think people with severe hay fever or household respiratory allergy will sometimes have urticarias when they inhale these antigens and they find their way into the circulation. Thus you could say that in some circumstances urticaria might occur as a contact dermatitis.

Dr. Schwartz. It is unlikely that one would have urticaria from an inhaled allergen without any respiratory symptoms. It is hard to think of a mechanism by which that would happen. It is important to establish the timing of symptoms when taking the history: If a patient has seasonal allergic symptoms for a few weeks of the year and has chronic urticaria for the whole year, that patient will of course have positive skin tests for seasonal allergy. However, the seasonal allergy and the urticaria do not seem to be related. I usually ask these patients if they think their urticaria is related to their seasonal allergies, and they will say no, they are not. The eye itching, nasal stuffiness, and sometimes the breathing go together, but the urticaria usually follows a different course.

I would conclude that we may be looking at two types of urticaria: either a contact urticaria or urticaria as part of a systemic reaction from inhaled allergens. That second presentation of urticaria would be part of a systemic reaction and not a reaction isolated to the skin.

Infectious diseases and urticaria

Dr. Cooper. Infectious diseases receive much attention as urticaria-associated diseases, but in fact the association

Volume 25
Number 1, Part 2
July 1991

is extremely rare. I still think that many antibiotics are prescribed to people on the basis of vaguely positive reactions. Pharyngeal cultures, antistreptolysin O, streptozyme antibody testing, and sinus and dental films are tests that are done commonly with some yield.

Dr. Soter. Jacobson et al.[1] analyzed every one of these tests, and the only useful one they found was the sinus film. However, later in a follow-up letter[2] they said that even sinus films were not helpful after all.

Dr. Cooper. So would you never recommend that a sinus film be taken?

Dr. Soter. I would not do it routinely. Obviously you might want it in an isolated incident.

Dr. Schwartz. I would not routinely do an infectious disease workup for urticaria. In the initial history, if the person is having fevers, sinus tenderness, nasal congestion, adenopathy, or diarrhea, you would do some of these tests early on. If they have photosensitivity, alopecia, or associated arthralgias, for example, you would consider an evaluation for collagen vascular disease. Depending on the history, you may or may not save the collagen vascular disease workup or infectious disease workup to the very end.

Dr. Cooper. No, you would start those workups earlier in those circumstances.

Dr. Schwartz. Suppose the patient has no weight loss, no fever, and normal complete blood counts, then I do not think you would have sinus films, and I do not think you would go on a wild goose chase for too many infections. Perhaps one would look for viral infection in some cases. To look for parasites in a patient with a normal eosinophil count and no gastrointestinal symptoms in whom everything else is normal is not likely to be fruitful.

Parasitic disease and urticaria

Dr. Greaves. We have many postgraduate doctors in the tropical countries, and they have challenged me about the frequency of urticaria in patients with parasites. They say it is not uncommon for patients to have urticaria and a normal eosinophil count but to have parasites in their gut. When they treat the parasitic disease, the urticaria improves. They have much more experience with tropical diseases than I have. My practice is that if you have a normal eosinophil count, do not bother with stool cultures for ova and parasites.

Dr. Soter. My experience is the same as yours. We have a number of people from tropical countries who visit our unit, and they tell me that I do not understand parasites. I may not, because we do not live in a primary endemic area.

***Candida* and HIV associated with urticaria**

Dr. Greaves. Two of my colleagues in Britain, Bob Warin and Bob Champion, have a series of papers in which they describe patients with chronic urticaria and clinical evidence of candidosis. They treated these patients, and of course, the urticaria improved. Then they went back to these patients and put a nasogastric tube into the stomach. Under total blinded conditions they infused *Candida* antigen and showed that the urticaria flared again. On the other hand, in my practice treating candidosis in patients with urticaria does not do the slightest good, and thus I am dubious. However, the literature is still there to justify it, and you can quote papers if anyone challenges you.

Dr. Schwartz. I have never seen urticaria associated with *Candida.*

Dr. Ellis. Do you see urticaria associated with HIV infections?

Dr. Soter. We do see it, but I do not think that any analysis has been done. I would not be surprised if HIV and urticaria are associated, but I cannot say that they are with any certainty.

Dr. Greaves. However, isn't drug-induced urticaria common in HIV-infected people?

Dr. Soter. It is not so much drug-induced urticaria, it is drug-induced morbilliform reactions. There is definitely an increased incidence of drug reactions but not of urticaria per se. It may well turn out that the incidence of urticaria is increased in patients with HIV, but it is too early to say.

RAST test in the workup of urticaria

Dr. Ellis. Dr. Schwartz, what do you think about the RAST test? How do you use it? What does it do for you?

Dr. Schwartz. I almost never use it, but not because I think it is a bad test. Ideally it is almost equivalent to skin testing in its sensitivity. It may miss certain conditions in which IgE is not continuously produced, so that serum levels could decrease. However, IgE may remain on the mast cell for many months. The quality of the RAST test depends very much on the antigens that are put on the disk, the coupling procedures involved, and the modifications that occur. Thus there are potential problems with the RAST test and also potential problems in deciding what is positive and what is not.

Skin testing clearly tells you whether that person has allergic reactivity, aside from the few false-positive cases. However, skin testing may be contraindicated in some individuals for example, those with severe eczema or dermographism.

I do not think that RAST testing is really controversial. If you have a good RAST test, it can be used instead of skin testing. I think you get into more trouble not with RAST testing but with IgG testing against foods to explain symptoms of urticaria or other conditions. Another pitfall is trying to use late-phase skin test responses to make a diagnosis. The late-phase reactions that sometimes occur may not always be from a late-phase allergic reaction. In some cases they can be irritant reactions. In-

tradermal food tests frequently produce irritant reactions and should not be done.

Thus I believe that one could use either a good RAST test or a good skin test appropriately and come up with a diagnosis of allergic risk. Neither test tells you that this is the cause of the allergy or the reaction. However, they can provide you with a measure of allergic risk.

REFERENCES

1. Jacobson KW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. JAMA 1980;243:1644-6.
2. Jacobson KW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. JAMA 1981;245:29-30.

The Diagnosis and Management of Urticaria: a Practice Parameter Part I: Acute Urticaria/Angioedema Part II: Chronic Urticaria/Angioedema

Editors:

Alan A Wanderer, MD; I Leonard Bernstein, MD; David L Goodman, MD; Richard A Nicklas, MD*; James T Li, MD; William E Berger, MD; Mark S Dykewicz, MD; Stanley M Fineman, MD; Rufus E Lee, MD; Jay M Portnoy, MD; Diane E Schuller, MD; and Sheldon L Spector, MD

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing *The Diagnosis and Management of Urticaria: A Practice Parameter.* This is a complete and comprehensive document at the current time. The medical environment is a changing environment and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology.

These parameters are not designed for use by pharmaceutical companies in drug promotion.

* This parameter was edited by Dr. Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

Reprint requests to:
Joint Council on Allergy, Asthma and Immunology,
50 N Brockway St, Ste 3-3,
Palatine, IL 60067

PUBLISHED PRACTICE PARAMETERS of the Joint Task force on Practice Parameters

Practice Parameters for the Diagnosis and Treatment of Asthma. J Allergy Clin Immunol (Nov) 1995;96:S707–S870.

Practice Parameters for Allergy Diagnostic Testing. Ann Allergy Asthma Immunol (Dec) 1995;75: S543–S625.

Practice Parameters for the Diagnosis and Management of Immunodeficiency. Ann Allergy Asthma Immunol (March) 1996;76:282–294.

Practice Parameters for Allergen Immunotherapy. J Allergy Clin Immunol (Dec) 1996;98:1001–1011.

Disease Management of Atopic Dermatitis: A Practice Parameter. Ann Allergy Asthma Immunol (Sept) 1997;79:197–211.

The Diagnosis and Management of Anaphylaxis. J Allergy Clin Immunol (June) 1998;1001:S465–S528.

Algorithm for the Diagnosis and Management of Asthma: A Practice Parameter Update. Ann Allergy Asthma Immunol (Oct) 1998;81:415–420.

Diagnosis and Management of Rhinitis: Parameter Documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol (Nov) 1998;81:S463–S518.

Parameters for the Diagnosis and Management of Sinusitis. J Allergy Clin Immunol (Dec) 1998; 102:S107–S144.

Stinging Insect Hypersensitivity: A Practice Parameter. J Allergy Clin Immunol (May) 1999;103: 963–980.

Disease Management of Drug Hypersensitivity: A Practice Parameter. Ann Allergy Asthma Immunol (Dec) 1999;83:665–700.

The Joint Task Force has made an intense effort to appropriately acknowledge all contributors to this parameter. If any contributors are inadvertently excluded, the Task Force will insure that appropriate recognition of such contributions is subsequently made.

EDITORS:

Alan A Wanderer, MD
Clinical Professor—Dept. of Allergy
University of Colorado Health Sciences Center
Denver, Colorado
Allergy & Asthma Consultants, PC
Englewood, Colorado

I Leonard Bernstein, MD
Clinical Professor of Medicine & Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio

David L Goodman, MD
Medical Director
Allergy & Asthma Consultants, PC
Englewood, Colorado

Richard A Nicklas, MD
Clinical Professor of Medicine
George Washington Medical Center
Washington, DC

James T Li, MD
Professor of Medicine
Director, Training Program in Adult Allergy/Immunology
Mayo Clinic and Medical School
Rochester, Minnesota

William E Berger, MD
Clinical Professor of Pediatrics
Division of Allergy and Immunology
University of California College of Medicine
Irvine, California

Mark S Dykewicz, MD
Associate Professor of Internal Medicine
Director, Training Program in Allergy and Immunology
St. Louis University School of Medicine
St. Louis, Missouri

Stanley M Fineman, MD
Clinical Assistant Professor of Pediatrics
Emory University School of Medicine
Atlanta, Georgia

Rufus E Lee, MD
Private Practice
Dothan, Alabama

Jay M Portnoy, MD
Chief, Section of Allergy, Asthma and Immunology
The Children's Mercy Hospital
Professor of Pediatrics
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

Diane E Schuller, MD
Professor of Pediatrics
Pennsylvania State University
Milton S. Hershey Medical College
Hershey, Pennsylvania

Sheldon L Spector, MD
Clinical Professor of Medicine
University of California—Los Angeles
Los Angeles, California

REVIEWERS:

Vincent S Beltrani, MD
Associate Clinical Professor
Department of Dermatology
Columbia University
New York, New York
Associate Clinical Professor
Department of Medicine
Division of Allergy, Immunology and Rheumatology
University Medical & Dentistry of New Jersey
Newark, New Jersey

Ernest N Charlesworth, MD
Clinical Associate Professor of Medicine
University of Texas Medical School at Houston
Shannon Clinic
San Antonio, Texas

Allen P Kaplan, MD
Medical University of South Carolina
Charleston, South Carolina

Chester T Stafford, MD
Professor Emeritus
Medical College of Georgia
Augusta, Georgia

ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY

Formerly published as ANNALS OF ALLERGY

Editor: Edward J O'Connell, MD
Mayo Clinic
411 Guggenheim Bldg
200 First St SW
Rochester, MN 55905
507-538-0009

The Annals of Allergy, Asthma, & Immunology is the Official Publication of the American College of Allergy, Asthma, & Immunology. It is published monthly by the American College of Allergy, Asthma, & Immunology

December, 2000

For submission of articles, see "Instructions for Authors"
Changes of address directed
to the ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY
should be sent to:
Jim Slawny, Executive Director
ANNALS OF ALLERGY, ASTHMA, & IMMUNOLOGY
Suite 550, 85 West Algonquin Road, Arlington Heights
Illinois 60005
Telephone – (847) 427-1200
email: mail@acaai.org

Annals of Allergy, Asthma, & Immunology (ISSN-1081-1206) is published monthly for $50.00 (US), $95.00 (all corporate/institution/subscription agency) and $98.00 (foreign) by the American College of Allergy, Asthma, & Immunology, 7212 Davis Ct, McLean, VA 22101. Periodicals postage paid at McLean, VA and additional mailing offices. (POSTMASTER: Send address changes to AMERICAN COLLEGE OF ALLERGY, ASTHMA, & IMMUNOLOGY, 85 West Algonquin Road, Suite 550, Arlington Heights, IL 60005.) Printed in the USA.

Preface

Urticaria is one of the most common dermatologic presentations. Acute urticaria is often associated with food, drug, or physical hypersensitivity, as well as pseudoallergic reactions. Because accompanying pruritus is often intense, most patients seek care from their primary care physicians who, in many instances, can determine probable cause by history, physical examination and a few simple laboratory tests. The mainstay of treatment is the use of a single H_1 antagonist or a combination of H_1 antagonists. Persistence of cutaneous lesions beyond 6 weeks is defined as chronic urticaria, for which etiology is more difficult to determine. Management of this chronic condition may also present a unique challenge.

Angioedema is swelling of subcutaneous (dermal) areas. It may or may not accompany urticaria. If acute angioedema involves glossopharyngeal or laryngeal tissues, it may be life-threatening. Similar to urticaria, it may become chronic. Angioedema induced by C1 esterase inhibitor deficiency is not associated with urticaria or pruritus.

This practice parameter consists of two parts: (1) a section on acute urticaria and (2) a section on chronic urticaria. Each part has its own diagnostic and management algorithm with referenced narrative annotations. These are designed to assist clinical decision making for both diagnosis and management. Clinical decision points are clearly shown and each of these proceeds stepwise to logical implementation strategies. Supplemental information in the form of commentaries and a list of references is provided for each part.

This parameter includes pertinent considerations about etiology, histopathology, differential diagnosis, and associated conditions. Special emphasis is placed on current principles of management.

The initial drafts of the acute and chronic urticaria/angioedema sections were prepared by Drs. David Goodman and Alan Wanderer, respectively. The data in these drafts were based on a detailed analysis of current publications in the peer-reviewed literature by Drs. Goodman and Wanderer. Extensive discussions of these drafts by the Joint Task Force on Practice Parameters resulted in consensus about the major body of recommendations, all of which were referenced by appropriate publications in the literature. Some of the material in this document could not be referenced in this fashion. When this situation arose, the Task Force reached consensus by considering the clinical experience of the Task Force as well as designated consultants. Peer review of the revised draft was conducted by independent board certified experts selected by the governing bodies of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Appropriate suggestions for modification that could be documented by literature sources by these individuals were then incorporated into the final draft of the document. *Consensus opinions for which evidence was ambivalent or controversial are italicized.*

The Joint Task Force is grateful to the co-spondoring organizations for financial support and encouragement. Special thanks and gratitude are acknowledged to those individuals who donated substantial time and effort in producing this document and, in particular, to Susan Grupe who shepherded the completion of this document.

Executive Summary

I. ACUTE URTICARIA/ ANGIOEDEMA

A recent episode of urticaria/angioedema lasting less than 6 weeks is characterized as acute, while lesions recurring for more than six weeks are termed chronic. In acute urticaria/angioedema, the etiology may be readily apparent to both the patient and the physician. For example, the patient who presents with acute urticaria after drug administration, insect sting, or repetitive physical triggers will often note an association. The longer the urticaria persists the more difficult it is to determine a specific etiology.

Urticaria should be considered when the patient presents with pruritic (and sometimes painful or burning), erythematous, circumscribed (or coalescent) wheals. Urticarial lesions commonly involve the extremities and trunk but may appear on any part of the body. In contrast to urticaria, angioedema presents as deeper subcutaneous swelling. Less circumscribed than the lesions of urticaria, angioedema has a predilection to areas of loose connective tissue such as the face or mucous membranes involving the lips or tongue. If angioedema involves the upper respiratory tract, life-threatening obstruction of the laryngeal airway may occur. Hereditary or acquired angioedema associated with C1 esterase inhibitor deficiency are particularly prone to this presentation, although other forms of angioedema can present either with laryngeal or glossopharyngeal edema causing hoarseness and difficulty in swallowing.

The etiology of urticaria/angioedema can often be deduced by a detailed history. The patient should be asked about recent use of medications (including herbals and supplements), food exposures, physical triggers, viral infections, contactants, occupational and natural allergen exposures or systemic diseases which can manifest as acute urticaria. The physical examination should include the skin, lymph nodes, eyes, ears, throat, neck, joints, lungs, heart, and abdomen in an effort to detect an underlying causal condition.

Findings ascertained by history or physical examination may direct attention towards an identifiable trigger or cause of urticaria/angioedema. Given the vast number of potential urticarial triggers and the difficulty in identifying them, any clues uncovered by history and physical may be extremely important. Evaluation of a suspected cause of acute urticaria/angioedema is often based on a clear temporal relationship between onset of symptoms and exposure to a specific food, insect sting or drug. If IgE-mediated penicillin-induced hives is suspected, predictive diagnostic skin tests are available. Allergy skin testing and/or in vitro tests may be useful in determining whether anaphylactogenic foods or inhalants are the cause of urticaria. Viral diagnostic studies may be helpful in confirming the association of hives with viral infections (eg, the Epstein-Barr virus). On the other hand, a complex evolving process may develop in patients with acute urticaria/angioedema. Initial evaluation may not provide definitive diagnosis and further management becomes empiric.

In the absence of historical information or physical signs suggesting an underlying cause, therapeutic intervention should be implemented. The immediate treatment of acute urticaria/angioedema that occurs as a component of anaphylaxis necessarily takes precedence over diagnostic considerations. Patients may improve after removal of factors that augment or induce urticaria/angioedema (eg, aspirin, NSAIDs, or alcohol ingestion). The cornerstone of treatment for acute urticaria/angioedema not associated with anaphylaxis is the use of H_1 antihistamines. Second generation H_1 antihistamines are usually preferred. When these fail, first generation antihistamines, such as hydroxyzine or diphenhydramine may be effective, although caution about the sedating side effects of these agents should be emphasized. The use of glucocorticosteroids in the treatment of patients with acute urticaria/angioedema is rarely necessary. If they are required, short courses of oral glucocorticosteroids rather than depot parenteral preparations are preferred to lessen the duration of systemic effects.

If known triggers or causes for urticaria/angioedema are not discovered within the first six weeks of the onset of symptoms, further evaluation and management of this chronic process becomes more complex. At this point, referral to an allergist/immunologist is appropriate, especially if the etiology has not been determined.

II. CHRONIC URTICARIA

Urticarial lesions are defined as chronic if manifestations persist or recur beyond six weeks. Persistent symptoms may be daily or episodic. Diurnal patterns are often reported but these are highly variable from patient to patient. It is not possible to predict the duration of chronic urticaria/angioedema. Spontaneous remissions often occur within 12 months but many patients continue to have symptoms at least periodically for years. Conditions that can masquerade as urticaria include erythema multiforme minor, nonspecific maculopapular exanthemata, mast cell releasibility syndromes such as urticaria pigmentosa and urticarial vasculitis. The skin lesions of urticarial vasculitis differ from urticaria in that they are palpable, purpuric, and persist 24 hours or longer. Resolution of these lesions is prolonged and they often leave residual pigmented changes in the skin.

If skin lesions have the appearance of urticarial vasculitis, a skin biopsy should be performed. Routine histopathology reveals the presence of leuko-

cytoclastic vasculitis while immunofluorescence may demonstrate the presence of fibrinogen, various immunoglobulins, and complement within the vascular lesions. Systemic collagen vascular diseases should also be considered in the differential diagnosis of urticarial vasculitis. Treatment of this condition may require various anti-inflammatory agents such as glucocorticosteroids, colchicine, dapsone, hydroychloroquine, or other cytotoxic agents.

Commonly, chronic urticaria and angioedema coexist; however, some patients may develop chronic angioedema without urticaria. Etiologic triggers of chronic angioedema without urticaria may be the same as those observed in acute urticaria and include medications, occupational exposures, insect sting, physical hypersensitivity disorders, delayed pressure angioedema, and C1 esterase inhibitor deficiencies. Drugs such as ACE inhibitors or aspirin/NSAIDs may induce or aggravate angioedema. If this relationship is suspected, the drug should be withdrawn as soon as possible.

Of particular importance is the family history, because of the possibility of hereditary C1 esterase inhibitor deficiency. The episodes of swelling in patients with this disease are often precipitated by trauma. Screening C4 levels should be obtained in all patients with chronic angioedema without urticaria. C4 levels are usually decreased during and between attacks while C2 levels are reduced only during attacks. Fifteen percent of patients with hereditary C1 esterase inhibitor deficiency have normal quantitative levels of C1 esterase inhibitor protein that is dysfunctional. Chronic angioedema due to C1 esterase inhibitor deficiency may also be acquired as a manifestation of a systemic connective tissue disease, a lymphoproliferative disorder or as a de novo autoantibody to C1 esterase inhibitor protein. The treatment choices for recurrent, life-threatening attacks of C1 esterase inhibitor deficiency are limited and supportive. Plasma infusions or C1 esterase inhibitor concentrates (available only on an experimental basis) may offer short-term palliative benefit. Should these measures fail, intubation or tracheostomy may be necessary. To prevent recurrent episodes of angioedema due to C1 esterase inhibitor deficiency, prophylactic management with anabolic steroids may be helpful.

It is very unusual to find an exogenous cause for chronic urticaria/angioedema. Nevertheless, every effort should be made to determine the etiology of these symptoms by redirecting attention to a detailed medical history and review of systems. Triggers such as foods, drugs, physical factors, insect bites, occupational exposures, and contactant exposures should have been ruled out during the initial workup of acute urticaria. The differential diagnosis of chronic urticaria/angioedema should include complement-mediated disorders, malignancies, cutaneous or systemic mastocytosis, mixed connective tissue diseases and cutaneous blistering disorders (eg, bullous pemphigoid and dermatitis herpetiformis). Only a few screening laboratory tests are possibly helpful in detecting etiology at this stage of the workup. These include a complete blood count with differential, erythrocyte sedimentation rate, urinalysis, and liver function tests. Since thyroid autoantibodies may be present in up to 28% of patients with urticaria/angioedema, particularly women with chronic urticaria/angioedema, some clinicians advocate that these tests be obtained regardless of the patient's thyroid status. Evaluation of the patient for autoantibodies to high affinity IgE receptor (Fc_eR1) should also be considered. If not previously obtained, a punch skin biopsy should also be performed in patients with difficult-to-manage chronic idiopathic urticaria. Two groups of patients with chronic urticaria have been identified based on the histopathology of the skin lesions: (1) perivascular lymphocyte-predominant urticaria and (2) perivascular polymorphonuclear-predominant urticaria. Patients with lymphocyte-predominant infiltrates are more responsive to antihistamine therapy. Patients with polymorphonuclear cell-predominant infiltrates are relatively resistant to antihistamines and will likely require more aggressive treatment such as oral glucocorticosteroids.

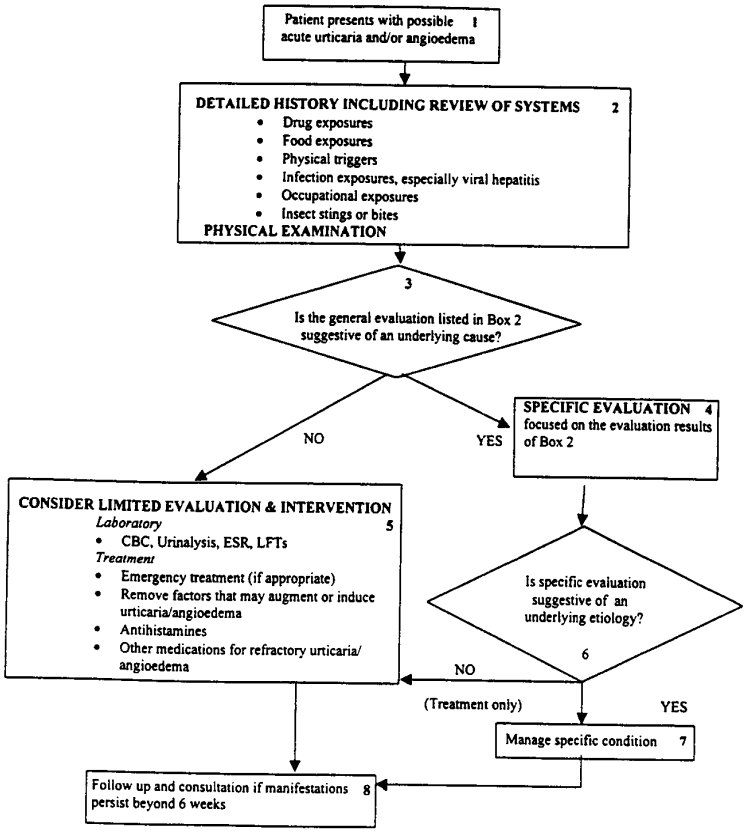
The management of chronic urticaria (with or without angioedema) should include elimination of specific or nonspecific agents that are known to exacerbate these conditions. For example, removal of urticarial aggravants such as aspirin, NSAIDs, or alcohol is advised. Rarely, specific treatments may be applicable if a causal trigger can be identified. In the vast majority of cases, management is necessarily oriented toward palliation of symptoms. For most patients, symptomatic treatment with H_1 antihistamines remains the mainstay of management. Sedation from first generation antihistamines may reduce the discomfort of pruritus associated with urticaria; however, first generation antihistamines may cause undesirable and potentially dangerous side effects related to sedation, including driving impairment and risk for fatal automobile accidents, decreased workplace productivity, increased risk for occupational accidents, and impaired learning and academic performance. Second generation antihistamines (loratadine, fexofenadine), at recommended doses do not have a sedative effect. Cetirizine may have a sedative effect in a small percentage of patients. $Beta_2$ agonists and calcium channel blockers are occasionally effective in treating urticaria/angioedema due to their ability to prevent release of mediators from mast cells. If symptoms become refractory, persistent, and interfere greatly with quality of life then various combinations of drugs can be considered. First and second generation antihistamines have been utilized in various combinations. A combination of H_1/H_2 antireceptor antagonists may be successful in some patients. If antihistamines are ineffective and symptoms significantly interfere with the patient's ability to function, glucocorticosteroids or other anti-inflammatory agents such as antileukotrienes, dapsone, colchicine, and even cytotoxic drugs may be consid-

ered. Some patients with thyroid autoantibodies may respond to small doses of thyroid hormone. A few patients with severe chronic urticaria associated with anti-$Fc_{\epsilon}R1$ receptor autoantibodies have improved after intravenous immunoglobulin therapy. The long-term management of refractory, chronic urticaria/angioedema is greatly facilitated when there is good rapport between physician and patient. Teaching the patient to become more observant about possible triggers may be helpful and has been widely recommended. Prolonged and detailed use of diaries has helped to identify triggers and give the patient a sense of participation, although these instruments rarely detect the cause and may lead the patient to develop an unhealthy obsession about his/her urticaria. Patient participation can be accomplished by reinforcement of the patient's adherence to the treatment regimen and continuous reassurance in the hope that urticaria/angioedema will spontaneously resolve.

THIS PAGE INTENTIONALLY LEFT BLANK.

Part 1: Acute Urticaria/Angioedema

ALGORITHM FOR ACUTE URTICARIA/ANGIOEDEMA



The following Annotations are detailed explanations of the Algorithm.

*** ANNOTATION 1: Patient presents with possible acute urticaria and/or angioedema**

Urticaria and/or angioedema are generally referred to as *acute* if they are of less than 6 weeks duration (see Algorithm for acute urticaria).[1] Acute urticaria occurs more commonly in children and young adults, whereas chronic urticaria is more common in "middle-aged" women.[2-5] It is useful to characterize urticaria as acute in a patient who is experiencing urticaria for the first time or who has had recurring acute urticarial events, versus the patient who has a history of urticaria for several weeks on a continuous basis. In the former group of patients, the etiology may be readily apparent to both the patient and the physician. For example, the etiology may be obvious in a patient who presents with acute urticaria after drug administration, an insect sting, or repetitively following exposures to cold. If the cause of an acute episode of hives is obvious to both patient and physician, a detailed history and physical are not required. **(Proceed to Annotation 3)** In contrast, the longer the urticaria has been continuously present, the more difficult the etiology is to determine.[6]

As many as 15% to 24% of the US population will experience acute urticaria and/or angioedema at some time in their lives.[7,8] Urticaria should be considered when the patient presents with pruritic (and sometimes painful or burning), erythematous, circumscribed (or coalescent) wheals. Urticarial lesions commonly involve the extremities and trunk but may appear on any part of the body. Angioedema manifests itself as deeper subcutaneous swelling. Less circumscribed than the lesions of urticaria, angioedema has a predilection for areas of loose connective tissue such as the face, eyelids or mucous membrane involving the lips, and tongue. If tissue distention involves sensory nerves, angioedema lesions may be painful or paresthetic.[2,9] Location and/or duration of the lesions may provide clues to the etiology of the process. Thus, lesions due to cold exposure, exercise or dermatographism typically last less than 2 hours and lesions of urticarial vasculitis appear predominantly on lower extremities and persist without change in morphology for longer than 24 to 48 hours.[10]

Clinical presentations of urticaria/angioedema may encompass dermatographism [ie, exaggerated triple response of Lewis (local reddening, edema and surrounding flare)], papular urticaria, localized urticaria, cutaneous and mucosal manifestations of anaphylaxis/anaphylactoid reactions or an underlying disease. Angioedema may occur with or without urticaria. In the latter circumstance, hereditary or acquired C1 esterase inhibitor deficiency should be suspected.

Acute urticaria and/or angioedema may begin suddenly, with physical manifestations appearing over a period of minutes to hours, or may evolve insidiously over a longer period of

time. The evanescent, transient time course of acute urticaria and/or angioedema lesions is characteristic of the process.[2,11]

If angioedema involves the upper respiratory tract, life-threatening obstruction of the laryngeal airway may occur. Hereditary or acquired angioedema associated with C1 esterase deficiency are particularly prone to this presentation, although other forms of angioedema can present with glossopharyngeal edema causing hoarseness and difficulty in swallowing.[2,12] Presentations such as this, however, accentuate the importance of evaluating the patient who presents with acute urticaria and/or angioedema for the need of emergency treatment, as urticaria and/or angioedema may be early signs in the evolution of anaphylaxis. A detailed history and physical examination may need to be deferred until emergency treatment has been administered.

*** ANNOTATION 2: Detailed History and Physical Examination**

To maximize the possibility of discovering the specific etiology of acute urticaria and/or angioedema, a detailed history of the circumstances preceding and surrounding the onset of the condition is necessary. This should include, but not necessarily be limited to, the following information: (1) current or previous medications, herbals, or supplements (including excipients) which the patient has used and the time they were started in relationship to the appearance of the lesions; (2) relationship to food exposures (ingestion, inhalation, contact) and the onset of urticaria and/or angioedema;[13] (3) relationship of potential physical triggers, eg, cold, exercise, heat, sweating, pressure, sun (or light) exposure; (4) exposure to infectious processes, such as a respiratory virus, viral hepatitis, or infectious mononucleosis; (5) occupational exposure to allergens or irritants; (6) any recent insect sting or bite; (7) contact exposure due to high or low molecular weight allergens; (8) allergen exposure by inhalation; and (9) a complete review of systems to include systemic diseases, such as autoimmune, connective tissue and lymphoproliferative disorders.[2,14,15-25]

A thorough physical examination should, at a minimum, include examination of the skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen in an effort to detect an associated underlying condition (eg, connective tissue disorders, thyroid disease, lymphoreticular neoplasms).[9,26] **(See Commentary 1).**

*** ANNOTATION 3: Is evaluation suggestive of an underlying cause?**

Specific findings on physical examination or clues developed from the clinical history may direct the evaluation towards an identifiable trigger for the urticaria and/or angioedema. Pertinent infectious exposures, food ingested within several hours prior to the appearance of symptoms several hours after ingestion, medication use preceding the appearance of lesions, or occupational exposures may allow the diagnostic focus to be narrowed to a few suspect triggers. These clues are important given the plethora of potential urticarial triggers and the inherent difficulty in identifying triggers responsible for sporadic urticarial reactions.[13] **(see Commentary 1)**

On examination, the presence of: thyroid enlargement (suggesting an autoimmune process and/or hormonal dysregulation); lymphadenopathy or visceromegaly (suggesting an underlying lymphoreticular neoplasm); or joint, renal, central nervous system, skin or serous surface abnormalities (suggesting a connective tissue disorder) will similarly focus the evaluation.[27] The presence of dermatographism (urtication on stroking of the skin) suggests the presence of a physical urticarial process.[28,29] Similarly, examination procedures directed to other suspected physical urticarias, (eg, cold, heat or solar urticaria/angioedema) can be employed for diagnosis.[30-34] Cold, heat, and light tests are available for these respective physical urticarias.[30-34] Localized hives or edema at pressure sites also point to a physical trigger for the urticarial process.[13] Pinpoint hives after exercise or heat exposure suggest a possible cholinergic process.[35] Concomitant manifestations of a more general process (eg, respiratory distress, hypotension, airway obstruction, gastrointestinal distress) accompanying urticaria should immediately redirect attention away from hives as the primary factor to an underlying anaphylactic process which necessitates rapid intervention.

Patients with acute urticaria and/or angioedema may represent a complex, multifactorial, evolving process. Evaluation, diagnosis, and management (both short-term and, if lesions persist beyond 6 weeks, long-term) may be challenging. For these reasons, patients presenting with acute urticaria and/or angioedema, for which the inciting triggers are not clear and easily avoided or initial therapy is not optimally effective, might be considered for referral to an appropriate specialist.

*** ANNOTATION 4: Specific evaluation**

The specific evaluation of a patient presenting with acute urticaria and/or angioedema should focus on the findings suggested by the clinical history and physical examination. Patients with a specific food, drug or insect hypersensitivity should be evaluated with appropriate diagnostic tests. For instance, a patient presenting with acute urticaria in temporal relationship to a specific food, insect sting/bite or drug may warrant in vivo or in vitro assessment of specific IgE (if available) to that particular allergen in a controlled setting where the expertise and equipment needed to treat an anaphylactic reaction are available. If acute mononucleosis is suspected, appropriate tests for Epstein-Barr virus (eg, Monospot™) could be confirmatory. The association of other infections with acute urticaria has not been sufficiently documented to recommend specific diagnostic tests.[36,37] A patient presenting with recurrent episodes of acute angioedema of the face, tongue or lips, in association with bouts of severe abdominal discomfort without associated urticaria should be evalu-

ated with specific complement studies to exclude hereditary or acquired C1 esterase inhibitor deficiency. Acute urticaria in association with the administration of penicillin or a related beta-lactam antibiotic may warrant diagnostic evaluation with penicillin skin testing. Allergen skin testing and/or in vitro tests for detection of specific IgE antibody to inhalants (eg, animal danders, pollens, molds, etc) may be useful when the history reveals that urticaria/angioedema occurs after direct contact with a suspected allergen such as direct contact with animals, weeds, and grass. Physical findings of weight loss, lymphadenopathy, and visceromegaly would warrant a further medical evaluation to exclude an underlying lymphoreticular malignancy.

*** ANNOTATION 5: Limited Evaluation/Treatment**

In the absence of historic or physical examination findings leading to a suggested underlying cause, a limited laboratory diagnostic evaluation (including a complete blood count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests) may be considered, primarily to identify occult underlying conditions at a stage prior to a more overt clinical presentation.[26] Concomitantly, or following such evaluation, interventional measures may be implemented. As previously stated, the immediate therapy of acute urticaria and/or angioedema as part of evolving anaphylaxis may necessarily take temporary precedence over diagnostic evaluation. Although there may be increased risks in elderly patients and patients with preexisting cardiovascular diseases, there are no contraindications to the use of epinephrine in acute life threatening situations. Removal of factors that may augment or induce urticaria/angioedema, (eg, NSAIDs or alcohol ingestion) may result in improvement and would thus seem appropriate in both acute and chronic presentations of urticaria/angioedema.[38]

Since histamine is one of the primary mediators of urticaria, antihistamine therapy comprises the cornerstone of therapy for acute presentations of this condition.[5] Continuous treatment with antihistamines over a period of weeks may suppress the urticarial process until a sustained remission occurs. With the advent of second-generation, low-sedating or non-sedating H_1-antihistamines, the impact of treatment on mental alertness and quality of life can be minimized, primarily through the avoidance of the daytime sedation associated with the use of first-generation H_1-antihistamines.[39–43] Use of second-generation H_1-antihistamines, (eg, loratadine, fexofenadine, or cetirizine) may be quite effective in controlling the urticarial process without side effects although cetirizine may be mildly sedating in some patients. **(see Commentary 2).** When necessary to achieve optimal hive and pruritus control, as-needed doses of first-generation H_1-antihistamines, (eg, hydroxyzine or diphenhydramine) may be added to or given in place of these agents.[44] Caution is warranted in carefully building up the dose of older, sedating antihistamines, especially in the treatment of patients involved in occupations that require the operation of machinery or vehicles, or where constant mental alertness cannot be compromised.[45–49] To facilitate necessary medication regimen adjustments, an open line of communication between patient and physician is essential during this initial phase of therapy. If optimal doses of H_1-antihistamines do not provide adequate hive control, H_2-antihistamines, (eg, ranitidine or cimetidine) may be added to the regime.[50] Tricyclic antidepressants such as doxepin, possessing more potent H_1 and H_2-antihistamine properties than some first-generation classical antihistamines, may have a role in therapy, although side effects such as dry mouth may limit their tolerability.[51]

The routine use of glucocorticosteroids in the treatment of patients with acute urticaria and/or angioedema is rarely necessary.[9] When considered essential for acute management, short courses of oral glucocorticosteroids rather than depot parenteral preparations are preferred, to lessen the duration of systemic effects.[52]

There are preliminary reports about the potential usefulness of leukotriene modifiers in the treatment of chronic urticaria.[53,54] Until such potential leukotriene-modifying approaches are evaluated in groups of acute urticaria patients, their clinical use remains empirical (although potentially justifiable for patients refractory to conventional therapies or in patients for whom avoidance of glucocorticosteroid therapy is desired).

*** ANNOTATION 6: Is additional evaluation suggestive of underlying etiology?**

In the proper clinical context, the finding(s) of specific, confirmatory laboratory data, [eg, a positive in vitro assay for a food allergen; a low C4 level; abnormal functional/quantitative assays of C1-esterase inhibitor protein; a positive skin test for penicillin; or an abnormal hemogram confirmed by specific hematologic investigations (bone marrow examination, abdominal CT, etc,) supporting the presence of an underlying lymphoreticular malignancy] may verify the initial diagnostic suspicions of particular specific etiologies for the urticarial process. If a cause has not been determined at this point, the associated chronicity and complexity of the underlying process and its clinical management may warrant referral to an appropriate specialist.

*** ANNOTATION 7: Manage specific condition**

When a specific etiology of the urticaria and/or angioedema has been identified, avoidance/elimination of the inciting trigger(s) assumes the central role (eg, avoidance of specific food allergens, drugs, or trauma that induces angioedema in a patient with hereditary or acquired C1 esterase inhibitor deficiency). Although the etiology of acute urticaria and/or angioedema may be easier to discover than that of chronic urticaria and/or angioedema, the cause or causes may still elude identification. The patient should be counseled regarding this issue, emphasizing the benign prognosis of the condition, provided that history, physical ex-

amination, or laboratory features do not suggest a more serious underlying process.

*** ANNOTATION 8: Follow up, if symptoms persist**

The persistence of urticaria and/or angioedema beyond 6 weeks, despite appropriate acute evaluation and intervention necessitates a reorientation towards a chronic process, and may thus warrant further evaluation discussed in the accompanying algorithm on evaluation of chronic urticaria and/or angioedema **(Part II)**. At this point, referral to an allergist/immunologist is appropriate, especially if the etiology has not been conclusively determined.

The following Commentaries (1 and 2) provide further details and references.

COMMENTARY 1: History and Physical Examination

The differential diagnosis of acute urticaria and/or angioedema must be kept at the forefront during the initial evaluation of the patient, as urticaria and/or angioedema, or lesions resembling these processes, may be the initial signs of systemic disease. Evaluation of the urticarial process should be characterized and correlated with associated historical elements.

The following underlying processes, many of which have prominent dermatologic findings, should be differentiated from urticaria.[26]

Erythema multiforme minor often involves lesions morphologically resembling urticaria, and is triggered by similar underlying disorders, eg, infections, drugs, or neoplasms. A more exaggerated prodromal phase, accompanied by fever, malaise, pharyngalgia, burning or stinging of the lesions and mucosal lesions may develop in those patients who progress to erythema multiforme or the Stevens-Johnson syndrome, potentially fatal processes.

Bullous pemphigoid and dermatitis herpetiformis are both autoimmune bullous/vesiculobullous processes. Early lesions in both diseases are often very pruritic and clearly have identifiable urticarial components, often resembling lesions of papular or cholinergic urticaria. The symmetry of the lesions of dermatitis herpetiformis, and the progression of the lesions of bullous pemphigoid to typical bullae, usually allow differentiation of these disorders.

Urticaria is often a component of serum sickness which is an IgM/IgG immune complex-mediated hypersensitivity response to drug exposure, insect stings, or heterologous serum administration. Immune complexes in slight antigen excess stimulate anaphylatoxin-mediated histamine release. Arthralgias, fever, and lymphadenopathy are prominent. The time course is slower in onset (days to weeks) than an acute, IgE-mediated anaphylactic response to these same potent triggers. Additionally, the other target organ manifestations of an acute anaphylactic reaction (eg, bronchospasm and hypotension) are not typically present.

Urticarial vasculitis may be restricted to the skin or be part of a systemic immune complex and/or autoimmune disorder. The specific clinical characteristics are individual lesions lasting longer than 24 hours, purpura, bruising, petechiae, livedo reticularis, predilection for the lower extremities (versus trunk or arms), pigmentation of lesions in various stages of healing, ulceration of lesions, predominance of burning and pain (versus pruritus), and systemic or constitutional symptoms such as fever, arthralgia/arthritis, gastrointestinal symptoms, myalgias, malaise, or weight loss. These features allow separation of this entity from a more benign urticarial process.

Mast cell releasability syndromes include (1) cutaneous mastocytosis [ie, urticaria pigmentosa, solitary mastocytoma, diffuse cutaneous mastocytosis (without urticaria pigmentosa), and telangiectasia macularis eruptiva perstans]; (2) systemic mastocytosis with or without skin involvement; (3) mastocytosis in association with hematologic disorders (eg, leukemia); (4) lymphadenopathic mastocytosis with eosinophilia; and (5) mast cell leukemia.[55] Flushing, hives, itching, bruising, and tingling are common cutaneous symptoms. Systemic symptoms are diverse depending on the amount and degree of visceral mast cell involvement. Darier's sign may be helpful in patients with cutaneous mastocytosis.

The morphology of the urticarial lesions may give clues to the underlying trigger(s). For example, cholinergic urticaria occurs after a rise of body core temperature (eg, after exercise, heat exposure, or fever). The lesions typically begin as small, generally 1 to 3-mm wheals, with large surrounding erythema ("flare"). In contrast, urticaria presenting in association with exercise-induced anaphylaxis characteristically has larger initial wheals. The delayed, point-of-exposure swelling and/or urticaria associated with pressure urticaria presents yet another variation in the appearance of the urticarial process.

Assessment of the prevalence of findings in a series of adult patients with urticaria and/or angioedema showed that urticaria and angioedema were present in tandem in approximately 50% of cases. In 40% of cases, urticaria was present without accompanying angioedema. In the remaining 10%, angioedema was exclusively present.[6] It is in this latter group that concern should be given to the possibility of either an underlying complement disorder such as a C1 inhibitor deficiency, or a non-immunologically mediated adverse drug reaction such as that seen with angiotensin-converting enzyme inhibitor (ACE) therapy. The concomitant presence of *both* urticaria and angioedema virtually eliminates the possibility of hereditary or acquired C1 esterase inhibitor deficiency. Isolated angioedema in the upper extremities should give rise to the consideration of an obstructive phenomenon such as the superior vena cava syndrome. The systemic capillary leak syndrome, which presents with brawny edema and shock, is an additional differential diagnostic consideration.[56,57]

A detailed history of infectious exposures, medication use (both prescription, over-the-counter, herbal, and other unconventional types), use of vitamins and dietary supplements, and food ingestion temporally related to the appearance of lesions is important.[58] Acute infections in children may be associated with acute urticaria.[36,37,59] Epstein-Barr virus (EBV), hepatitis (A, B, and C),[60-63] and gastrointestinal parasites have been implicated anecdotally in the causality of urticarial reactions. Food proteins incriminated in the precipitation of acute allergic urticaria include peanuts, nuts, fish, shellfish, wheat, eggs, milk, soybeans, and fruits. Food additives such as benzoates, sulfites, monosodium glutamate, butylated hydroxyanisol, butylated hydroxytoluene, FD&C approved dyes and others have been implicated in some cases of urticaria.[64-66] Non-immunologic high content of or release of histamine causing hives and flushing may occur after ingestion of strawberries, cheese, spinach, eggplant, lobster, and tomatoes.[67] Bacterial conversion of histidine to high levels of histamine may occur in contaminated scombroid fish (eg, tuna, mackerel). Among the most common medication triggers of urticaria are penicillin, other beta-lactam antibiotics, opiates, radiocontrast media, aspirin, insulin, and many other non-beta lactam drugs and biologics. **[See Disease Management of Drug Hypersensitivity: A Practice Parameter (Ann Allergy Asthma Immunol 1999;83:S665–S700)].**

A social and travel history should be obtained to highlight possible infectious exposures encountered during travel, or acute allergen exposures in the patient's home or workplace. Occupational history may discover contact allergen exposure (eg, chromates in the cement industry, latex, other rubber products, and cosmetics) amenable to identification by patch testing with the appropriate allergen(s).[68-70] Exposure to plants and common aeroallergens may suggest a source of symptoms secondary to contact exposure.[71-75]

COMMENTARY 2: Representative Agents and Doses for the Treatment of Acute Urticaria

Cetirizine (Zyrtec):
5 to 20 mg, once daily or occasionally in divided doses especially if somnolence is not a problem†

Loratadine (Claritin):
5 to 10 mg once daily in AM

Fexofenadine (Allegra):
180 mg given once daily or 60 mg twice daily

Hydroxyzine HCl: (Atarax or Vistaril):
10 to 100 mg daily often at bedtime or in divided doses, titrated to effect or somnolence.

Diphenhydramine (Benadryl):
12.5 to 100 mg per dose q4 to 6 hour PRN

Doxepin: (Sinequan)
Adults: 25 to 100 mg/day
Adolescents: 25 to 50 mg/day initially up to a maximum of 100 mg/day
Children: 1 to 3 mg/kg/day

†Julian L. et al. Cetirizine in the treatment of chronic urticaria Clin Ther 1991;13:81–85.

REFERENCES

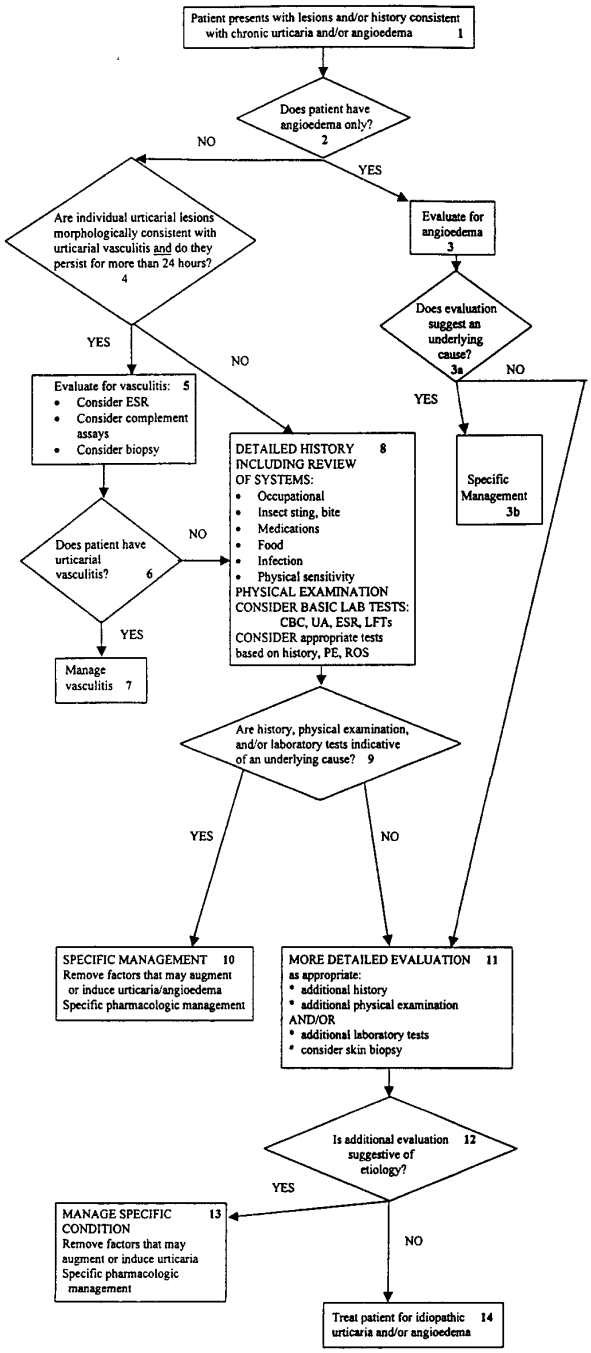
1. Soter, NA. Acute and chronic urticaria and angioedema. J Am Acad Dermatol 1991;25:146–154.
2. Monroe EW, Jones HE. Urticaria: an updated review. Arch Dermatol 1977; 113:80–90.
3. Margolis CF, Nisi R. Urticaria in a family practice. J Fam Pract 1985;20: 57–64.
4. Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138(4):635–638.
5. Champion RH, et al. Urticaria and angio-oedema: a review of 554 patients. Br J Dermatol 1969;81: 588–597.
6. Sheldon HM et al. The vexing urticaria problem: present concepts of etiology and management. J Allergy 1954;25: 525–560.
7. Mathews KP. Urticaria and angioedema. J Allergy Clin Immunol 1983; 72:1–18.
8. Ledford DK. Urticaria and angioedema. chpt 12. In: Allergic diseases: diagnosis and treatment. Totowa, NJ: Lieberman P, Anderson JA, eds. Humana Press, 1997.
9. Friedmann PS. Assessment of urticaria and angioedema. Clin Exp Allergy 1999(Suppl 3):109–12;113–115.
10. Aoki T et al. Acute urticaria: history and natural course of 50 cases. J Dermatol 1994;21(2):73–77.
11. Donaldson VH, Bernstein DI, Wagner CJ, et al. Angioneurotic edema with acquired C1 inhibitor deficiency and autoantibody to C1 inhibitor: response to plasmapheresis and cytotoxic therapy. Children's Hospital Research Fdtn, 1991;397–
12. Kaplan AP: Urticaria and Angioedema. Ch. 79 In *Allergy: Principles and Practice*, 5th ed. 1998, Mosby, Toronto.
13. Asthesson RA, Sontheimer R. Urticarial vasculitis and syndromes in association with connective tissue disease. Ann Rheum Dis 1991;50:743–4.
14. Wuthrich B: Food-induced cutaneous adverse reactions. Allergy 1998; 53(Suppl 46):131–135.
15. Drenkard C, Villa AR, Reyer E, et al. Vasculitis in systemic lupus erythematosis. Lupus 1997;6:235–42.
16. Yell JA, Mbuagvaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosis, Br J Dermatol. 1996;135:355–62.
17. Kulp-Shorten CI, Callen JP. Urticaria, angioedema and rheumatologic disease. Rhem Dis Clin North Am. 1996; 22:95–115.
18. Laman SGD, Provost TT. Cutaneous manifestations of lupus erythematosis. Rheum Dis Clin North Am. 1994;20: 195–212.
19. Asthesson RA, D'Cruz D, Stephens CJ, et al. Urticarial vasculitis in a connective tissue disease clinic: patterns, presentations and treatment. Semin Arthritis Rheum 1991;20:285–96.
20. deCastro FR, Masouye I, Winkelmann A, Saurat JH. Urticarial pathology in Schnitzler's (hyper-IgM) syndrome. Dermatology 1996;193:94–9.
21. Polliack A, Lugassy G. Autoimmunity and autoimmune syndromes associated with and preceding the development of lymphoproliferative disorders. Leukemia. 1992;6:152–4.

22. Cartwright RA, Darwin C, McKinney PA, et al. Acute myeloid leukemia in adults: a case-control study in Yorkshire. Leukemia. 1988;2:687–90.
23. Theirs BH. Dermatologic manifestations of internal cancer, CA Cancer J Clin. 1986;36:130–48.
24. Zuraw BL. Urticaria, angioedema and autoimmunity. Clin Lab Med 1997;17: 559–69.
25. Charlesworth EN: The spectrum of urticaria: All that urticates may not be urticaria. Immunol & Allergy Clin NA 1995;15(4):641–658.
26. Vaughn MP et al: Urticaria associated with systemic disease and psychological factors. Immunol & Allergy Clin NA 1995;15(4):725–744.
27. Casale TB et al: Guide to physical urticarias. J Allergy Clin Immunol 1988;82:758–763.
28. Duke WW: Urticaria caused specifically by the action of physical agents. JAMA 1924;83:3–9.
29. Wanderer AA. Cold urticaria syndromes; historical background, diagnostic classification, clinical and laboratory characteristics, pathogens, and management. J Allergy Clin Immunol. 1990;85:965–81.
30. Chang A, Zic JA. Localized heat urticaria. J Am Acad Dermatol 1999;41: 354–6.
31. Alora M, Taylor CR. Solar urticaria: case report and phototesting with lasers. J Am Acad Dermatol 1998;38: 341–3.
32. Kyckaert S, Roelandts R. Solar urticaria: a report of 25 cases and difficulties in phototesting. Arch Dermatol. 1998;134:71–4.
33. Schafer CM: Physical Urticaria. Immunol & Allergy Clin NA 1995;15(4): 679–699.
34. Hirschmann JV et al: Cholinergic urticaria: A clinical and histologic study. Arch Dermatol 1987;123: 462–467.
35. Schuller DE, Elvey SM. Acute Urticaria Associated with Streptococcal Infection. Peds 1980;65:592–
36. Schuller DE. Acute urticaria in children: Casuses and an aggressive diagnostic approach. Postgrad Med 1982;72:179.
37. James J, Warin RP: Chronic urticaria: The effect of aspirin. Br J Dermatol 1970;82:204–205.
38. Rihoux JP, Donnelly F, Burton B. The clinical efficacy of H1 antagonists in urticaria and rhinitis. J Allergy Clin Immunol 1998;102:33–4.
39. Monroe EW. Loratadine in the treatment of urticaria. Clin Ther 1997;19: 232–42.
40. Spencer CM, Foulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs 1993;46:1055–80.
41. Finn AF Jr, Kaplan AP, Fretwell R, Qu R, Long J. A double blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol. 1999; 104:1071–8.
42. Kalivas J et al: Urticaria: Clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. J Allergy Clin Immunol 1990;86:1014–1018.
43. Simons, FER. The antiallergic effects of antihistamines (H1-receptor antagonists). J Allergy Clin Immunol 1992; 90:705–715.
44. O'Hanlon JF, Reammers DIG. Antihistamine effects on actual driving performance in a standard test. A summary of the Dutch experience. 1989–1994. Allergy 1995;50: 234–242.
45. Gengo FM, Manning C. A review of the effects of antihistamines on mental processes related to automobile driving. J Allergy Clin Immunol 1990;186: 1034–1039.
46. Adelsberg BR, D'Amico-Beadone A. The effects of loratadine, diphenhydramine and placebo on worker productivity. Results of a double blind trial. J Allergy Clin Immunol 1990;85:296.
47. Vuurman EFPM, van Veggel LMA, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993; 71:121–126.
48. Kay GG, et al. Self-reported sedation doesn't predict impaired CNS functioning after dose of sedating antihistamine. J Allergy Clin Immunol 1999; 103(1 pt 2):S254.
49. Mansfield LE et al: Greater inhibition of dermographia with a combination of H1 and H2 antagonists. Ann Allergy 1983;50:264.
50. Green SL et al: Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. J Am Acad Dermatol 1985;12:669–675.
51. Pollack CV Jr, Romano TJ: Outpatient management of acute urticaria: the role of prednisone. Ann Emerg Med 1995; 26(5):547–551.
52. Spector S, Tan RA. Antileukotrienes in chronic urticaria (letter). J Allergy Clin Immunol 1998;101:572.
53. Ellis MH. Successful treatment of chronic urticaria with leukotriene antagonists. J Allergy Clin Immunol 1998 Nov;102:876–877.
54. Metcalfe DD. Classification and diagnosis of mastocytosis: Current status. J Investigative Derm 1991;96:2S–4S.
55. Atkinson JP, Waldmann TA, Stein SF, et al. Systemic capillary leak syndrome and monoclonal IgG gammopathy. Medicine 1977;56:225–239.
56. Amoura Z, Papo T, Ninet J, et al. Systemic capillary leak syndrome. Report on 13 patients with special focus on course and treatment. Am J Med. 1978;103:514–519.
57. Zuberbier T et al: Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Derm Venereol 1996; 76(4):295–297.
58. Halpern SR: Chronic hives in children: An analysis of 75 cases. Ann Allergy 1965;23:589.
59. Scully LJ, Ryan AE: Urticaria and acute hepatitis A virus infection. Am J Gastroenterol 1993;88(2):277–278.
60. Liutu M, Kalimo K, Uksila J, Kalimo H. Etiologic aspects of chronic urticaria. Int J Dermatol 1998;37: 515–519.
61. Hadzeyannis SJ. Skin diseases associated with hepatitis C infection. J Eur Acad Dermatol Venereol 1998;10: 12–21.
62. Schwaber MJ, Zlotogorsiki A. Dermatologic manifestations of hepatitis C infection. Int J Dermatol 1997;36: 251–254.
63. Goodman DL et al: Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). J Allergy Clin Immunol 1990;86:570–575.
64. Wuthrich B et al: Disulfite-induced acute intermittent urticaria with vasculitis. Dermatology 1993;187(4): 290–292.
65. Weiner M, Bernstein IL. Adverse reactions to drug formulation agents. A handbook of excipients. 1989; pp.253–340. Pub. Marcel Dekker, New York, NY.
66. Feldman JM. Histaminuria from histamine rich foods. Arch Intern Med 143: 2099–2102, 1983.
67. Kanerva L, Tokkanen J, Jolanki R,

Estlander T. Statistical data on occupational contact urticaria. Contact Dermatitis 1996;35:229–233.
68. Judd L. A descriptive study of occupational skin disease. NZ Med J. 1994; 107:147–149.
69. Taylor JS. Latex allergy update: four vignettes. Am J Contact Dermat 1998; Vol 9 No. 1:45–48.
70. Rietschel RL, et al. Guidelines of care for contact dermatitis. J Am Acad Dermatol 1995;32:109–113.
71. Rietschel RL. Human and economic impact of allergic contact dermatitis and the role of patch testing. J Am Acad Dermatol 1995;33:812–815.
72. Gerth van Wijk R, de Groot H. Occupational allergy caused by flowers. Allergy 1998;53:204–209.
73. Munoz FJ, Delgado J, Palma JL, Gimenez MJ, et al. Airborne contact urticaria due to mulberry (Morus alba) pollen. Contact Dermatitis 1995;32:61.
74. Vidal C, Cabeza N. Contact urticaria due to eucalyptus pollen. Contact Dermatitis 1992;26:265.
75. Spitalny KC, Farnham JE, Witherell LE, et al. Alpine Slide Anaphylaxis. N Eng J Med 1984;310:1034–1037.

Part II: Chronic Urticaria/Angioedema

ALGORITHM FOR CHRONIC URTICARIA/ANGIODEMA



The following Annotations are detailed explanations of the algorithm.

ANNOTATION 1: Does patient exhibit skin lesions consistent with chronic urticaria and/or angioedema?

Urticaria is characterized by pruritic, erythematous, blanching, circumscribed macular or raised lesions involving the superficial layers of skin. Urticarial lesions classically wax and wane and do not persist in a given location for more than 24 hours. Such lesions are defined as chronic if manifestations are persistent or recurring over 6 weeks in duration (Fig. 1b).[1-5] Persistent symptoms may be daily or episodic (weekly, monthly, etc). Diurnal patterns are often reported but these are highly variable from patient to patient. It is not possible to predict the duration of chronic urticaria/angioedema. Spontaneous remissions often occur within 12 months but a substantial number of patients continue to have symptoms at least periodically for years. Conditions that can masquerade as urticaria include but are not limited to the following entities: erythema multiforme minor, non-specific maculopapular exanthems, and mast cell releasability syndromes such as urticaria pigmentosa, (**see Commentary 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria** for details). Hypersensitivity vasculitis (ie., urticarial vasculitis) should also be excluded[6-9] (**see Annotations 4–6**). The skin lesions of urticarial vasculitis present with an urticarial appearance, but differ in that they persist 24 hours or longer in the same area, and may be palpable and purpuric. Following resolution, these lesions may leave residual pigmented changes in the skin. Urticarial vasculitis may be limited to the skin or be part of a systemic disorder.[1,6] On occasion, patients with pruritus alone are referred for urticaria evaluation[10] (**see Commentary 1** for

details). Angioedema involves swelling of deep subcutaneous regions in the skin and/or mucous membranes, such as a finger, hand, lip, tongue etc. There are many conditions that can masquerade as angioedema that must be considered when evaluating this skin manifestation[11] (**see Commentary 1 of Acute Urticaria and Commentary 1 of Chronic Urticaria** for details).

ANNOTATION 2: Does patient have chronic angioedema without urticaria?

Commonly, patients experience the coexistence of chronic urticaria and angioedema. However, some patients may present with chronic angioedema without urticaria. Patients with this manifestation fall into a separate category that may require diagnostic evaluations for unusual conditions[11] (**see Annotation 3**). The evaluation should move to **Annotation 4** if there is urticaria with angioedema.

ANNOTATION 3: Evaluation of chronic angioedema without urticaria

A detailed history, and physical examination are suggested to rule out underlying causes. Of particular importance is the family history because of the possibility of hereditary angioedema. Etiologic triggers include medications (eg, ACE inhibitors[12]) occupational exposure (eg, latex sensitivity)[13]; insect sting reactions[14,15]; physical hypersensitivity disorders (eg., cold urticaria that can present with generalized or regional angioedema following cold exposure[16]); exercise-induced angioedema with or without anaphylaxis[17,18]; pressure-mediated sensitivity that can cause angioedema of the feet following walking or running[19] and less often food hypersensitivity.[20–23] The managing physician may require the expertise of an allergist/clinical immunologist to evaluate unusual causes of angioedema (**see Annotation 8** for other etiologies).

A history of angioedema alone may suggest a rare disorder of C1esterase inhibitor deficiency, which may be inherited as a autosomal dominant or acquired angioedema due to C1esterase inhibitor deficiency may present as an acute episode of regional swelling following trauma (eg, dental manipulation of the oropharynx) or episodic abdominal pain which is thought to be secondary to angioedema involving the intestinal tract.[24,25,26] Although C1 esterase inhibitor deficiency may present as an acute episode, detailed history may confirm the recurrent nature of these disorders. It is advised that screening C4 levels be obtained on all patients with chronic angioedema without urticaria, especially patients with the aforementioned history. C4 levels are usually decreased during both symptomatic and asymptomatic periods of the disease, while C2 levels are reduced only during attacks.[24] If the C4 level is reduced, quantitative C1 esterase inhibitor levels should be obtained. If these levels are normal, a functional assay should then be done. Fifteen percent (15%) of patients with hereditary C1esterase inhibitor deficiency have evidence of dysfunctional inhibitor protein with normal quantitative levels of C1esterase inhibitor.[27,28]

Patients with chronic angioedema without urticaria may have acquired C1esterase inhibitor deficiency associated with a lymphoproliferative disorder or a systemic connective tissue disease.[24] A reduced C1q in association with decreased C1 esterase inhibitor and C4 warrants evaluation for an occult lymphoproliferative disorder. The presence of C1q autoantibody and/or C1 esterase inhibitor autoantibody suggests an underlying connective tissue disease although it may be present without evidence of an underlying disease.[29–31] C1q autoantibody is sometimes associated with lupus erythematosus.[32–34]

ANNOTATION 3a: Is evaluation of chronic angioedema without urticaria suggestive of an underlying cause?

Appropriate laboratory testing is advised for confirmation of a specific cause of angioedema without urticaria. For example, a history of recurring angioedema of the hands after exposure to latex gloves requires an in vitro blood test (ie, ELISA, dot blot) and/or a carefully applied skin prick/puncture test with latex protein.[13] Screening for the C4 complement component should be obtained for suspected C1esterase inhibitor deficiency.[24] An individual who experiences swelling of the lips after eating cold foods should have a localized (ice cube) cold stimulation test to diagnose cold-induced urticaria/angioedema.[16] Other examples of laboratory confirmation are described in **Commentary 3**. On occasion, a suspected cause of angioedema without urticaria can only be established by history. Examples are angioedema caused by drugs such as ACE inhibitors[12] or aspirin/NSAIDS. There are no reliable in vitro tests that can confirm a drug-associated etiology. If there is a crucial need for the drug, a more definitive relationship of cause and effect can be obtained by withdrawal of the suspected drug followed by a double blind challenge format.[35] This procedure should be performed by physicians with expertise in monitoring this test.

ANNOTATION 3b: Specific management of an underlying cause of chronic angioedema without urticaria

Individuals with recurrent angioedema that is a manifestation of anaphylaxis should carry an emergency epinephrine kit (eg, Epipen).[36] In addition, specific management should be instituted once an etiology of angioedema without urticaria has been established. Latex-induced angioedema would require elimination of latex exposure and possible removal of cross-reacting food allergens from the patient's diet (eg, banana, avocado, grapes, peaches, apricots, cherry, pineapple, kiwi, chestnut, etc).[13] Recurring urticaria/angioedema due to cold sensitivity requires avoidance of cold exposure, particularly immersion (eg, aquatic activities) and possible prophylaxis with cyproheptadine, second generation antihistamines or doxepin.[16]

The treatment choices for recurrent acute life threatening attacks of C1esterase inhibitor deficiency (hereditary or acquired) are limited and usually supportive. *Some clinicians advocate treatment with plasma infusions or C1esterase inhibitor concentrates although the latter are not commercially available.*[37,38] Should these measures fail, intubation or tracheostomy may be necessary. For frequent episodes of angioedema due to C1 esterase deficiency, prophylactic management is possible with anabolic steroids (eg, Danazol or Stanazolol®[24]). Because of the danger of trauma-induced exacerbations, short-term prophylactic anabolic steroids 4 to 5 days prior to elective dental or surgical procedures should be considered.[39] **Annotations 10, 13, 14** discuss nonspecific considerations for treatment of angioedema with or without urticaria.

ANNOTATION 4: Do patients with chronic urticaria (with or without angioedema) exhibit lesions suggestive of urticarial vasculitis?

Although the prevalence of urticarial vasculitis is low, it is nevertheless important to recognize because this disease can be associated with other systemic conditions (ie, the Henoch-Schönlein syndrome) and is amenable to effective treatment. If skin lesions have an urticarial appearance and last longer than 24 hours in the same location, urticarial vasculitis (ie, hypersensitivity vasculitis) should be considered.[4,6–9] Typically these urticarial-like lesions: (1) are less pruritic and more painful than observed with true chronic urticaria, (2) are more prominent on lower extremities, (3) may be palpable and purpuric, and (4) following resolution may leave pigmented changes in the skin. Angioedema may accompany urticarial vasculitis.[40] In addition, urticarial vasculitis may be associated with systemic symptoms such as low-grade fever, arthralgia/arthritis, gastrointestinal complaints, pulmonary and ocular symptoms.[4,6–9,41] Urticarial vasculitis is thought to be due to immune complex mediated inflammation (**see Commentary 2** for details on mechanism). The evaluation should move to **Annotation 8** if urticarial lesions remain less than 24 hours in the same location.

Occasionally, history and examination may not provide definitive evidence of urticarial vasculitis. If urticarial vasculitis is suspected, it may be necessary to evaluate specific lesions at 24 hours, 36 hours, and 48 hours after the initial evaluation. Specific lesions should be circled and numbered as part of the ongoing assessment. Lesions that remain fixed beyond 24 hours require further diagnostic evaluation for urticarial vasculitis (**see Annotation 5**).

ANNOTATION 5: Evaluation of suspected urticarial vasculitis

If urticarial vasculitis is suspected, a punch biopsy of a suspected skin lesion should be obtained. Urticarial vasculitis lesions reveals a specific histopathology described in **Annotation 6**. Immunofluorescence of the skin biopsy may determine the presence of fibrinogen, immunoglobulin (eg, IgA, IgG, and IgM) and/or complement deposition, several or all of which are indicative of immune complex mediated events.[6–9] Other tests that may be useful include complement assays to rule out complement depletion (eg, CH50, C3, Factor B, and C1q)[7,8] and cryoglobulins. Immune complex assays (Raji assay and C1q binding) have limited sensitivity and specificity.[8,42] The erythrocyte sedimentation rate and/or C-reactive protein may be elevated in urticarial vasculitis.

ANNOTATION 6: Does patient have urticarial vasculitis?

The diagnosis of urticarial vasculitis is confirmed by the histopathologic results of the skin biopsy.[6,43] This includes polymorphonuclear infiltration within the walls of blood vessels and in the perivascular space. Leukocytoclasia (ie, fragmentation of neutrophils) is frequently noted along with endothelial swelling, red blood cell extravasation and fibrin deposition. Complement levels (eg, CH50) may be normal or decreased in this condition. Hypocomplementemia associated with urticarial vasculitis has a worse prognosis and is suggestive of systemic disease.[6] A decreased C1q level may be a sensitive marker of complement activation in patients with urticarial vasculitis. If there are decreased complement indices and/or C1q levels, a more thorough evaluation for systemic disease involving the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems should be considered.[43] Other serious diseases should be considered in the differential diagnosis of vasculitis[6–9,43] (**see Commentary 2**).

ANNOTATION 7: Management of urticarial vasculitis

Patients with urticarial vasculitis should be managed by physicians with expertise in these conditions. Antihistamines may be useful in managing the pruritus associated with urticarial vasculitis[9] (**see Annotation 14**). Other symptoms due to immune complex-mediated inflammation may not respond to antihistamine therapy. Patients with moderate or severe cutaneous disease, especially those with systemic manifestations, may require treatment with anti-inflammatory agents, such as: glucocorticosteroids, indomethacin, colchicine, dapsone and hydroxychloroquine.[6] Cytotoxic agents (eg, methotrexate,[44] azathioprine,[45] cyclosphosphamide[6]) can be used cautiously to reduce the dose requirements of corticosteroids. Patients receiving these medications require careful monitoring for potentially serious side effects associated with use of these agents.

Patients with urticarial vasculitis should be monitored for evidence of systemic disease that might affect the renal, gastrointestinal, pulmonary, ocular, and musculoskeletal systems. For example, periodic urinalysis and creatinine clearance (if indicated) should be performed to rule out renal involvement. Referral to a nephrologist may be indicated if significant and progressive renal abnormalities are detected. Annual ophthalmological referrals may also be appropriate.

ANNOTATION 8: Evaluation of chronic urticaria (with or without angioedema) to include detailed history, review of systems, physical examination and basic laboratory tests

It is unusual to find an exogenous cause for chronic urticaria/angioedema.[46,47] Nevertheless, every effort should be made to determine the etiology of these symptoms, especially by periodically obtaining a detailed history. Despite frustrating statistics, that a cause can only be confirmed in 5% to 20% of patients, it is helpful to evaluate patients based on broad categories of mechanisms[4,41,47] such as: IgE-dependent mechanisms (eg, drug, food, insect venom, and latex exposure); and complement-mediated mechanisms (eg, hereditary angioedema and serum sickness). The evaluation should include a detailed history of: (1) medications administered for several weeks before and during the onset of symptoms; and (2) symptoms temporally related to ingestion of food(s). At the time of evaluation, most patients will already have considered foods as a cause for their urticaria, either on their own or on the advice of a physician. In the vast majority of adult cases, attempts at identifying a food allergen are unsuccessful.[46] Other factors for consideration include (1) physical hypersensitivity[48]; (2) underlying infection[49,50]; (3) an autoimmune etiology[41,51,52]; (4) *possible hormonal effects,[41,53-55] especially when hives in women occur on a cyclic basis*; (5) manifestations consistent with malignancy[41]; (6) pertinent occupational exposure[56]; (7) multiple/repetitive or late onset reactions to insect stings/bites[14,15]; (8) direct contact of skin or oropharynx with foods,[57] chemicals,[58] animal saliva, and other substances; (9) familial pattern that might suggest hereditary syndromes[4]; and (10) psychologic stresses that might aggravate skin manifestations[41] (**see Commentary 3** for more history details).

A detailed review of systems is warranted to uncover symptoms that may suggest a systemic disease etiology for chronic urticaria/angioedema.[41] Multisystem symptoms involving joints, gastrointestinal tract, pulmonary, renal or ocular systems could suggest a systemic disease associated with urticaria/angioedema (eg, vasculitis, collagen vascular disease). A complete physical examination may provide unsuspected clues to the etiology of chronic urticaria/angioedema. The physical evaluation should include all systems to rule out serious underlying diseases (eg, malignancies, mixed connective tissue diseases, chronic hepatitis, chronic infections, cutaneous or systemic mastocytosis, cryoglobulinemia, etc). Association with other skin lesions may be helpful in the differential diagnosis of chronic urticaria; thus, residual discoloration of fading urticaria especially on the legs suggests urticarial vasculitis. Concomitant bullous eruptions would suggest cutaneous blistering conditions such as bullous pemphigoid or dermatitis herpetiformis. Reddish tan pigmented macules that urticate on stroking would suggest urticaria pigmentosa. Palpable purpura on lower extremities is seen with cryoglobulinemias or leukocytoclastic vasculitis. Specific physical findings in the skin or other systems may direct the diagnostic evaluation.

Laboratory test confirmation is essential if an etiology is suspected by history and/or physical examination. If they have not already been obtained, basic laboratory tests are advised as a screening approach for underlying diseases. The panel might include a CBC, ESR, urinalysis and liver function tests. *Because thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) and anti-Fc_ε1 receptor antibodies are being reported with increasing frequency, some clinicians recommend that these tests be obtained if the initial screening panel is noncontributory and the urticaria/angioedema persists.*[52,59-61] Other tests could be added to the screening panel based on clinical indications. Specific laboratory tests should be selective and based only on diagnostic suspicions (**see Commentary 3** for more testing details). If, at the initial presentation, chronicity of the patient's symptoms is already established in terms of months or years, it is justified to proceed directly to the next level of evaluation described in **Algorithm Box 11 and Annotation 11**. Under these conditions, evaluation of possible autoantibodies (eg, thyroid, anti-high affinity, Fc_ε1 receptor), as described above, and/or histopathologic data could be useful adjuncts in deciding optimal management (**see Algorithm Box 10 and Annotation 10**). **Commentary 3** also provides additional information about other possible helpful diagnostic pathways to detect triggers of mast cell activation at this stage of the patient's evaluation.

ANNOTATION 9: Is the evaluation of chronic urticaria (with or without angioedema) indicative of an underlying cause?

An underlying cause may be determined after data have been accumulated and are consistent with the history, physical examination and laboratory tests. Refer to **Commentary 3** for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

ANNOTATION 10: Specific management of chronic urticaria (with or without angioedema)

The management of urticaria/angioedema will, in part, be dictated by the etiology. For example, avoidance of offending antigens when identified (eg, drugs, foods, venom from insect stings, latex, etc)[1-5,11,13] applies to generalized and localized contact urticaria caused by antigen-induced IgE mechanisms. Non-specific agents that are known to exacerbate urticaria/angioedema (aspirin, NSAIDS,[62,63] opiates, alcohol); physical stimuli that cause symptoms such as cold, heat, deep pressure, exercise, solar radiation, etc should be avoided. Several physical hypersensitivity syndromes[48] respond to specific therapeutic regimens. Idiopathic (ie, primary) acquired cold urticaria[16] responds to prophylactic treatment with a variety of first generation antihistamines (in particular, cyproheptadine and hydroxyine), second

generation antihistamines (loratadine, fexofenadine, and cetirizine) and tricyclic antidepressants (doxepin).[16] Cholinergic urticaria can be treated with various antihistamines.[64,65] Delayed pressure urticaria is treated with first and second generation antihistamines and may require courses of oral glucocorticosteroids (eg, daily or if possible, every other day treatment) or other regimens including dapsone, NSAIDS, and sulfasalazine.[48,66,67] Selected cases of exercise-induced urticaria with or without anaphylaxis may require prophylactic treatment with first and/or second generation antihistamines which may help to reduce the frequency and/or intensity of attacks.[36,68] A prescription for an emergency epinephrine kit (eg, Epipen) is advised for individuals with a concomitant history of anaphylaxis or laryngeal angioedema. In addition, occult food or drug allergies in combination with exercise may induce symptoms.[69-71] In such cases, it is advised that patients avoid food or drug ingestion several hours before and after exercise. Dermatographism is best managed by patient awareness not only concerning the relationship of hives to scratching but also the need for prophylactic treatment with antihistamines.[72] It may be necessary to treat a suspected infectious disease associated with urticaria and/or angioedema, such as hepatitis C, with alpha interferon and/or ribavirin.[73] Treatment of an autoimmune disorder associated with urticaria/angioedema is dictated by the specific autoimmune disease. For example, treatment of autoimmune thyroid disorders with thyroid hormone may be associated with improvement or remission of urticaria.[59-61] Therapy of urticaria/angioedema occurring with other generalized diseases is dictated by the specific underlying condition (eg, neoplasms, systemic vasculitis, collagen vascular disorders, etc).

In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms. In general, removal of potential urticarial aggravants such as aspirin, NSAIDS, or alcohol is advised regardless of the underlying etiology. For most patients, symptomatic treatment with H_1 antihistamines remains the mainstay of management.[74,75] Sedation from first generation antihistamines may be desirable for reducing the discomfort of pruritus associated with urticaria. First generation antihistamines, however, may cause undesirable and potentially dangerous side effects including driving impairment and risk for fatal automobile accidents[76,77] decreased workplace productivity,[78] increased risk for occupational accidents, increased risk for falls in nursing home patients, and in children, impaired learning and academic performance.[79] Importantly, studies have demonstrated that many patients may not perceive performance impairment from first generation antihistamines, and that there is no correlation between subjective perception of sedation and objective performance impairment.[80] In contrast, second generation antihistamines (loratadine, fexofenadine, and cetirizine) at recommended doses are associated with minimal risk for these adverse effects, although cetirizine may have mild sedative effects. Accordingly, the decision to choose between first and second generation antihistamines for treatment of urticaria should consider these differences.

Both first and second generation antihistamines also exhibit anti-allergic and anti-inflammatory effects but such properties do not consistently contribute to the overall clinical responses induced by this class of drugs.[75,81,82] Combinations of various antihistamines and alternative therapeutic regimens such as glucocorticosteroids, other anti-inflammatory agents, β_2 agonists, calcium channel blockers and anti-leukotriene drugs are discussed in **Annotation 14**.

ANNOTATION 11: Further evaluation of chronic urticaria (with or without angioedema)

A more detailed review of the history, review of systems, and physical examination may be warranted to uncover a previously unrecognized underlying condition associated with urticaria/angioedema. The discovery process may in part require the physician's careful observation of the urticaria/angioedema process over a protracted period of time. New observations may emerge that can provide clues to an underlying diagnosis. Teaching the patient to become more observant may be helpful and has been widely recommended. For example, prolonged use of detailed diaries has been used in an attempt to identify triggers and give a sense of participation in care. This process rarely detects a cause and may lead the patient to develop an unhealthy obsession with his/her urticaria. On the other hand, patient participation can be accomplished by reinforcing the patient's adherence to treatment recommendation in the hope that the hives will spontaneously resolve. The long-term management of refractory chronic urticaria/angioedema is greatly facilitated when there is good rapport between physician and patient because continuous reassurance is required.

New observations may dictate more detailed review of systems, physical examination and specialized laboratory evaluation. For example, a patient may develop symptoms of hypothyroidism in association with chronic urticaria. A careful examination of the thyroid would then be advised along with tests to evaluate thyroid function and presence of autoimmune thyroid disorders (ie, anti-thyroid peroxidase/anti-thyroglobulin antibodies and autoimmune panels).[59-61] Since one or both thyroid autoantibodies may be present in up to 28% of patients with chronic urticaria/angioedema, some clinicians advocate that these tests be obtained, especially in women or in those patients with a family history of thyroid or other autoimmune disease.[83] In other situations, the managing physician might consider other tests depending on assessment of new or additional information. For example, hematologic leukemic markers might be ordered in a patient with acquired cold urticaria with cryoglobulinemia in order to rule out an underlying chronic lymphocytic leukemia process.[84] Imaging procedures may be helpful at this juncture, depending on the need to evaluate a

specific anatomical region in more detail. As part of the on-going re-evaluation, repeat or more detailed multisystem screening blood test panels may be indicated.

Other areas of evaluation may include trial elimination diets initially and/or limited food specific IgE tests (ie, percutaneous skin tests; in vitro tests) if foods are implicated by history or diary data as potential causes of the symptoms. In this situation, prick/puncture tests are preferable, provided dermatographism is not present. Positive food specific IgE tests would in turn suggest further confirmatory food elimination trials. Open-single or double-blinded placebo-controlled food, food additive, or drug challenges may also be useful.[85,86] These challenge procedures require close monitoring for symptoms of anaphylaxis.

A skin test with autologous serum may reveal a wheal and erythema response suggesting the presence of anti-IgE or anti high affinity IgE receptor antibodies.[52,87]

A body of clinical evidence is emerging that recommends a punch skin biopsy be performed on patients with difficult to treat chronic idiopathic urticaria. Two groups of chronic urticaria have been defined by skin biopsy results: (1) perivascular lymphocyte-predominant urticaria and (2) perivascular polymorphonuclear—predominant urticaria (ie, neutrophils, scattered eosinophils and mononuclear cells).[88,89] Several interesting clinical observations have been associated with each group.[90] Patients with lymphocyte-predominant infiltrates are more responsive to antihistamine therapy. Patients with polymorphonuclear cell-predominant infiltrates are relatively resistant to antihistamines and will more likely require oral glucocorticosteroid treatment. In addition, patients having IgG anti-IgE or IgE receptor autoantibodies often exhibit evidence of perivascular polymorphonuclear cell-predominant infiltrates in skin biopsies.[89] Eosinophil activation may occur later or be more persistent in patients without autoantibodies.[91] The skin biopsy may also detect unsuspected urticarial vasculitis or mastocytosis. The latter requires metachromatic stains such as Giemsa or toluidine blue for detection of increased numbers of mast cells (usually >4 per high power field).

ANNOTATION 12: Is additional evaluation of chronic urticaria (with or without angioedema) indicative of an etiology?

An underlying cause may be determined after data has been accumulated and analyzed from the history, physical examination, and laboratory tests. For example a skin biopsy might reveal unsuspected urticaria pigmentosa with evidence of mast cell aggregates revealed by metachromatic stains.[92,93] Other examples might be evidence of symptom induction during open-single or double-blinded placebo-controlled food, food additive or drug challenges.[85,86,94] At this juncture, the managing physician decides whether an underlying etiology has been established. Refer to **Commentary 3** for other causal relationships suggested by history, physical examination and confirmatory laboratory tests.

ANNOTATION 13: Management of specific etiology of chronic urticaria (with or without angioedema)

The management of urticaria/angioedema will, in part, be dictated by the specific etiology. For example, if a skin biopsy reveals either urticaria pigmentosa or mastocytosis, treatment would be tailored to this diagnosis and should include avoidance of trigger factors (eg, friction) and non-specific mast cell releasing agents (eg, alcohol, aspirin, opiates etc).[93] Specific pharmacologic therapy might include combinations of antihistamines, cautious use of cycloxygenase inhibitors, photochemotherapy with oral 8-methylpsoralen (ie, PUVA), and/or oral disodium cromoglycate[93,95,96] for bullous mastocytosis and gastrointestinal manifestations of systemic mastocytosis. Another example would be identification of a food as a possible cause demonstrated by an open single-blinded food challenge or a double-blinded placebo-controlled challenge. The managing physician would eliminate the putative food from the patient's diet.[85,86] It is important to recognize that isolation of a food substance as a cause of chronic urticaria/angioedema is rare. Refer to **Annotation 10** for more examples of specific management strategies dictated by diagnosis of an underlying disorder. In addition to specific treatment of an underlying condition, management should be oriented towards palliation of symptoms which is also described in **Annotation 10**. For most patients, symptomatic treatment with antihistamines is advised and described in **Annotation 10**. If indicated, the use of glucocorticosteroids and other anti-inflammatory agents is outlined in **Annotation 14**.

ANNOTATION 14: Treatment of chronic idiopathic urticaria (with or without angioedema)

At this stage of the evaluation it is reasonable to define chronic urticaria/angioedema as idiopathic since this is a diagnosis by exclusion of underlying etiologies. If treatment is ineffective up to this point, referral to an allergist/clinical immunologist or dermatologist might be considered. The therapeutic management should first be oriented towards palliation of symptoms which is discussed in **Annotation 10**.

Combinations of various antihistamines may be useful in suppressing symptomatology. These include (1) first generation H_1 antihistamines, (2) combinations of first and second generations using non-sedating agents in the morning and first generation drugs at night,[74] (3) combinations of second generation antihistamines, (4) combination of an agent with both H_1 and H_2 anti-receptor activity (ie, doxepin) with a first or second generation antihistamine, and (5) combination of an H_2 anti-receptor antihistamine [eg, cimetidine (Tagamet) or ranitidine (Zantac)] with a first or second generation antihistamine.[74] Managing physicians should acquaint themselves with the side effects, as discussed in **Annotation 10**, and drug-drug interactions

when using any combination of pharmacological agents.

Antihistamines may not be entirely effective in controlling urticaria because other capillary permeability inducing mediators are released (eg, leukotrienes; prostaglandin D_2; kinins; platelet activating factor, etc). Glucocorticosteroid treatment may be appropriate when antihistamines are not effective.[4] These agents are helpful in controlling the inflammatory cell influx that can potentiate the urticaria by secondary release of histamine releasing factors and cytokines. Managing physicians should explain the potential side effects associated with glucocorticosteroids. In some clinical situations, the managing physician or patient may request more evidence to justify the initiation of glucocorticosteroid therapy. A skin biopsy with perivascular predominant-polymorphonuclear cell urticaria may justify initiation and continuation of glucocorticosteroid treatment.[97] As soon as possible, glucocorticosteroid therapy should be discontinued or reduced to minimal requirements such as an every other day regimen to reduce potential side effects. On rare occasions, chronic urticaria/angioedema may not respond to prednisone. *Empirically, some of these patients may respond to methylprednisolone (eg, Medrol).*[64]

Alternative management and therapeutic regimens may be necessary in refractory forms of chronic urticaria/angioedema. *Mast cell degranulation inhibitors* [ie, *an oral beta-adrenergic agonist such as terbutaline or albuterol; an H_1 antihistamine such as ketotifen (not available in the US)*[74];] *may have a role in treatment of refractory conditions. Nifedipine, a calcium channel blocker may be of some benefit in controlling symptoms, either alone or in combination with antihistamines. Preliminary reports suggest that anti-leukotrienes may be effective in treating some patients with chronic idiopathic urticaria.*[98] There are anecdotal reports that oral cyclosporine,[99] colchicine,[100] or dapsone[100] may be helpful in selected cases of severe refractory chronic urticaria/angioedema. Repeated plasmapheresis over a 2-month period may be effective in controlling refractory chronic urticaria especially in patients with circulating IgG autoantibody to IgE or the high affinity IgE receptor.[101,102] A recent report described the efficacy of intravenous immunoglobulin therapy in patients with severe chronic urticaria caused by circulating autoantibodies.[103]

Glossopharyngeal and laryngeal angioedema deserve special attention as they may become life threatening or present as manifestations of anaphylaxis. Patients may present with other symptoms of anaphylaxis that may require emergency treatment, as discussed in **Annotation 5 of Acute Urticaria**. The mainstay of treatment for this emergency is epinephrine in doses dependent on the patient's age.[36] Intramuscular administration of epinephrine in children has been shown to produce a faster time of action than subcutaneous administration.[104] Other treatment modalities include parenteral H_1 and/or H_2 antihistamine antagonists and parenteral glucocorticosteroids. Close monitoring of vital signs and oxygen measurements (eg, pulse oximetry; arterial blood gases) may be necessary, as rarely a patient (eg, hereditary or acquired C1 esterase inhibitor deficiency) may require intubation to overcome a compromised airway.

The following Commentaries (1, 2, and 3) provide further details and references

COMMENTARY 1: Differential diagnosis of chronic urticaria, angioedema and pruritus

Erythema multiforme minor is often preceded by prodromal symptoms of malaise, fever, sore throat, muscle aches, arthralgia followed by pleomorphic cutaneous responses (ie, macular, papular, frequently iris or target-like lesions, and rarely urticaria).[2] More importantly, the lesions of erythema multiforme minor do not wax and wane; rather they remain fixed, are more frequently acral in distribution and usually burn or sting in contrast to urticarial lesions which are pruritic. Papular eruptions secondary to insect bites tend to occur on lower extremities and/or other exposed areas and persist longer than urticaria. Urticaria pigmentosa should be considered in the differential diagnosis of chronic urticaria if linear bead-like urticaria is induced by stroking over pigmented macular lesions (Darier's sign).[93]

Pruritic disorders can be erroneously assumed to be caused by urticaria. Chronic pruritus can be associated with systemic diseases[10] involving the renal, hepatic and/or thyroid systems, diabetes mellitus, polycythemia vera, lymphoproliferative disorders, neoplasms, xerosis, pregnancy, and psychiatric disorders.

Conditions masquerading as angioedema[11] are varied and physicians handling angioedema must be aware of the following systemic disorders: fluid overload, trauma, systemic capillary permeability syndrome,[105,106] venous obstruction (eg, facial edema caused by superior venal caval syndrome), contact dermatitis, serum sickness, parotid gland obstruction, infection, myxedema, chronic inflammatory disease of autoimmune origin such as dermatomyosistis, malignancies, lymphedema, chronic granulomatosis and/or infiltrative diseases such as sarcoidosis, amyloidosis and granulomatous angioedema involving the lips and perioral regions (ie, Melkersson-Rosenthal syndrome[107]). Psychogenic pseudo-angioedema should also be considered in the differential diagnosis.[108,109]

Angioedema and/or urticaria can be early warning manifestations of anaphylactic reactions. The occurrence of anaphylaxis can be established retrospectively if serum beta-tryptase levels are elevated.[110] This blood test should be obtained within 2 hours of the onset of anaphylactic symptoms although elevated tryptase levels may persist for 4 hours or longer after the appearance of symptoms. Elevation of alpha-tryptase (by subtracting beta-tryptase from total tryptase) is indicative of diffuse cutaneous or systemic mastocytosis.[111]

COMMENTARY 2: Immunopathology of urticarial vasculitis and underlying disease states associated with urticarial vasculitis

Urticarial vasculitis is thought to be due to immune complex mediated inflammation.[4,6] Complement is activated leading to anaphylatoxin (C3a, C5a) production. Anaphylatoxins bind to mast cell receptors causing mast cell degranulation and vasoactive mediator release. Urticaria/angioedema results from the increased capillary permeability effects of released vasoactive mediators. Neutrophil infiltration results in part from immune complex induction of neutrophil chemotactic factors (C5a).[6]

Urticarial vasculitis may be associated with disorders such as connective tissue diseases[112] (eg, rheumatoid arthritis, lupus erythematosus, and Sjögren's syndrome); serum sickness; infectious diseases such as chronic viral hepatitis (A[113], B[114], and C[115]), Lyme disease; myelomas, cryoglobulinemias and Schnitzler's syndrome (bone pain, fever, fatigue, weight loss, leukocytosis, anemia, elevated sedimentation rate, and IgM macroglobulinemia). Medication-induced vasculitis (eg, the Churg-Strauss syndrome) should also be considered in the differential diagnosis of this condition.

COMMENTARY 3: Detailed history and laboratory testing for evaluation of chronic urticaria (with or without angioedema)

A. History

A history is essential for determining the etiology of chronic urticaria/angioedema. It should include questions related to specific etiologic considerations.

A thorough drug history[1] should be elicited and include medications administered at least 1 month prior to and up to onset of symptoms. For example, penicillin administered 2 to 4 weeks prior to onset of symptoms can be responsible for serum sickness presenting with urticaria.[116] ACE inhibitors,[12] aspirin, other NSAIDS[63] can exacerbate and/or cause chronic urticaria and/or angioedema.

A food diary and history of temporal relationship of symptoms to food ingestion may occasionally elicit an unsuspected food or food additives as a cause of chronic urticaria/angioedema,[85,86] but this is a rare finding.

Chronic urticaria and/or angioedema may be associated with physical hypersensitivity disorders[48] such as cold-induced urticaria[16] and/or angioedema, which is one of the most common physical urticaria disorders; delayed pressure-induced urticaria; dermatographism; vibratory-induced urticaria/angioedema[48]; localized heat-induced urticaria; cholinergic urticaria[48] (characterized by fine papular urticaria associated with exercise or passive body warming that does not progress to anaphylaxis); aquagenic-induced urticaria[117]; solar-induced urticaria[45]; and exercise-induced anaphylaxis which is often associated with giant urticaria, angioedema, respiratory distress, gastrointestinal symptoms, hypotension and syncope.[71] If this entity is suspected, a detailed food and drug history[69] is advised to rule out food or drug as a co-factor. Apart from delayed pressure urticaria, the physical urticarias are pathogenetically unrelated to chronic urticaria because they usually last less than 2 hours and they do not demonstrate either lymphocytic or polymorphonuclear perivascular cellular infiltrates.

The history should determine the presence of underlying infections. *Chronic infectious illness as an etiology of chronic urticaria and/or angioedema is very controversial and is primarily based on anecdotal evidence of single case reports.* However, there is evidence to suggest an association between chronic viral infections such as hepatitis (A[113], B[114], and C[115]) and serum sickness and/or urticarial vasculitis. In addition, other viral diseases can be associated with chronic urticaria induction (eg, acquired cold urticaria with infectious mononucleosis).[118,119] *There are anecdotal reports associating chronic bacterial infections (eg, sinus, wounds etc) as causes of urticaria/angioedema, possibly via bacterial activation of complement.*[50] *Other infectious illness that has been associated with chronic urticaria/angioedema include chronic fungal infections, especially tinea pedis,*[120] *and chronic parasitic infestations.*[41] However, an extensive workup for occult bacterial and/or fungal infections is not justified.

The history should consider the possibility of an autoimmune etiology. Autoimmune disorders are occasionally associated with chronic urticaria and/or angioedema. Examples include: autoimmune-induced thyroiditis associated with anti-thyroid peroxidase antibodies[59-61]; systemic lupus erythematosus; and mixed connective tissue disorders. Autoimmunity may underlie chronic idiopathic urticaria.[52,53,87] There is evidence of IgG anti-IgE autoantibodies and also IgG autoantibodies to the high affinity IgE receptor on the mast cell (ie, IgG anti-FcεRI). This mechanism may explain the persistence of chronic urticaria/angioedema despite the absence of a specific exogenous sensitizing antigen.

The history should consider hormonal dysfunction. Hormone-induced disorders associated with chronic urticaria/angioedema include urticaria associated with pregnancy [ie, pruritic urticarial papules and plaques of pregnancy (PUPP)[121]], *urticaria associated with menstrual hormonal changes,*[53-55] and autoimmune thyroid disorders with evidence of antithyroid autoantibodies.[59-61]

The history may suggest the presence of an underlying malignancy. The association of malignancy, particularly lymphoreticular, and chronic urticaria/angioedema is based primarily on individual case reports.[49] Pruritus without urticaria may also be associated with malignancy.

Occupational history is necessary to rule out work exposure to sensitizing antigens such as latex,[13] as well as antibiotics, or chemicals in health, pharmacy or other occupations. Latex sensitivity may also develop after various types of nonoccupational exposure.

A history of exposure to insect stings/bites is essential. Particular attention should focus on the type of insect (eg, vespids[14,15], honey bee[14,15], fire ant[122]), and the physical consequences of the sting/bite. Rarely, late onset reactions to insect venoms may involve immune complexes manifested by angioedema, nephropathy and/or central nervous system signs.[123,124]

The history should elicit the presence of contact-induced urticaria. Contact-induced urticaria may be caused by latex exposure in gloves[13]; handling foods such as nuts, fish, or shellfish; direct handling or contact with sensitizing chemicals such as penicillin,[125] formaldehyde[126] in clothing; and by animals licking salivary proteins onto skin. In most cases contact urticaria is acute although patients exposed to contact allergens on a recurrent basis may present with a chronic history.

A family history should be elicited to rule out genetic forms of urticaria/angioedema[4] such as Muckle Wells syndrome[127] (urticaria, deafness, amyloidosis); delayed cold-induced urticaria[16] and hereditary angioedema (**see Annotation 3**).

The history should rule out psychologic factors that could aggravate chronic urticaria/angioedema.[108] Depressed or anxious individuals and elderly individuals with dementia may chronically irritate xerotic, dermographic skin, causing repeated outbreaks of urticarial-like lesions.

The history may suggest a metabolic cause for chronic urticaria. For example, there are several well-documented case reports describing the temporal eradication of chronic urticaria following parathyroidectomy for primary hyperparathyroidism.[128,129]

B. Laboratory

Laboratory tests for chronic urticaria/angioedema should be selective depending on specific historical considerations. Although it has been proposed that a highly sensitive penicillin-allergic patient could develop urticaria/angioedema after unsuspected exposure to penicillin in cow's milk, the current clinical evidence for this is unimpressive.[130-132] Depending on clinical circumstances, the workup might include skin testing to both the minor (minor determinant mixture or penicillin G) and major determinant of penicillin (Pre-Pen) and/or complement tests (eg, CH50; C1q binding or Raji immune complex assay; cryoglobulins)[41] to determine presence of immune complex-mediated serum sickness. Drug skin testing by skin prick/puncture or intracutaneous methods should be performed by physicians with expertise in interpretation of the results who have experience in handling adverse reactions (ie, anaphylaxis). On occasion, drug challenges may be necessary to clarify a causal relationship with a suspect drug.[116] Oral drug challenges should be performed by physicians with experience in this procedure (eg, allergist/clinical immunologist) using an open challenge or placebo-double blind format.

As emphasized previously, it is extremely rare to demonstrate a causal relationship between chronic urticaria/angioedema and the detection of specific IgE antibodies to food antigens either by skin tests or in-vitro tests.[85,86] Thus, except under rare circumstances, skin testing or in vitro tests for food-specific IgE antibodies are not indicated, and if done, should be selective based on historical correlation. Other in vitro tests (eg, food-specific IgG or IgG 4 antibody tests) are not reliable for evaluation of this condition.[133] Further, food elimination diets are generally not helpful in alleviating chronic urticaria/angioedema. Food challenges may be useful in eliminating concerns about food/additive induction of chronic urticaria/angioedema. Food challenges should be performed by physicians with experience in this procedure, using open challenge or a placebo-controlled single or double-blind format.

Laboratory testing for physical hypersensitivity disorders depends on the suspected disorder.[16,48] Cold testing for cold urticaria requires application of a cold stimulus (eg, ice cubes in a plastic bag) to the forearm. Wheal induction occurs after the cold stimulus is removed and the skin re-warms. Unfortunately direct cold application may be negative in atypical forms of cold urticaria. A history of light pressure sensitivity may require scratching the skin surface to induce dermographism. Deep pressure urticaria is verified by application of a weight strapped to the shoulder or thigh of a patient with this condition (eg, 15 lb in weight for 15 minutes).[48] Deep swelling will often appear 2 to 12 hours after application of the weight. Application of a vibratory stimulus to the skin can be used to elicit vibratory urticaria. Exercise testing under monitored conditions may be necessary to rule out exercise-induced urticaria/anaphylaxis and cholinergic urticaria, which produces classic punctate urticaria. Other physical factors that may induce urticaria (eg, heat, solar, and aquagenic stimuli) require specific clinical diagnostic tests.

The likelihood of uncovering an infectious illness as a cause of chronic urticaria/angioedema is minimal. Nevertheless, there are data in the literature to support investigation under certain circumstances. Laboratory testing depends on the suspected disorder. Laboratory evaluation for hepatitis (A[113], B[114], and C[115]) and infectious mononucleosis[122,123] might be useful if one of these diseases is suspected. Radiologic evaluation of specific anatomical regions to rule out chronic occult infection is not indicated unless there are convincing supportive clinical data. On rare occasions stool testing for ova and parasites and skin scraping for suspected tinea infection may be helpful.[3,120]

Autoimmune-induction of chronic urticaria/angioedema requires laboratory confirmation. The presence of anti-thyroid peroxidase antibodies in euthyroid or hypothyroid states may implicate an autoimmune etiology.[59-61] An evaluation for an underlying autoimmune mechanism may require an anti-nuclear antibody panel. Intracutaneous skin tests with autologous serum may induce a wheal and flare reaction that is suggestive of circulating autoantibodies to IgE/IgE receptors.[87]

Tests for malignancy will depend on data accumulated from the history/

physical examination. A chest x-ray[11] might confirm the presence of a tumor and/or mediastinal widening in patients with suspected superior venal caval obstruction who present with chronic swelling of the face and neck. A lymphoreticular neoplasm should be suspected[41] in patients with cryoglobulinemia and acquired cold urticaria.

A history suggesting a potential occupational cause for chronic urticaria, such as hives occurring when wearing latex gloves, might necessitate laboratory tests such as latex specific in vitro tests for latex proteins and/or skin tests to latex proteins.[13]

Venom-specific IgE and IgG RAST and/or venom skin tests should be ordered if the history of insect sting-induced urticaria/angioedema is documented. Serum sickness and/or urticarial vasculitis arising from a hymenoptera sting would require complement assays or other tests for immune complexes. The venom skin tests should be performed or supervised by an experienced allergist/immunologist.

Specific IgE antibody tests (ie, percutaneous skin tests and specific in vitro tests; patch tests read 15 to 30 minutes after application) to suspected antigens[134–139] may be useful in confirming a causal relationship between a contactant and induction of urticaria/angioedema. However, contact urticaria is usually acute rather than chronic.

Specific procedures should be ordered if there is a possibility of hyperparathyroidism as causative of chronic urticaria. Appropriate tests would include total calcium, ionized calcium, parathyroid hormone levels and bone density.[128,129]

REFERENCES

1. Greaves MW. Chronic urticaria. N Engl J Med 1995;322:1767–1772.
2. Charlesworth EN. The spectrum of urticaria. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15:641–657.
3. Mathews KP. Urticaria and angioedema. J Allergy Clin Immunol 1983; 72:1–14.
4. Kaplan AP. Urticaria and angioedema. In: Middleton E, Reed CE, Ellis EF, et al, eds. Allergy, principles and practice. 5th edition 1998: 1104–1122.
5. Wanderer AA. Urticaria and angioedema. In: Friedman HH, ed. Problem-oriented medical diagnosis. 4th edition 1987:29–33.
6. Venzor J, Baer SC, Huston DP. Urticarial vasculitis. In: Charlesworth EN, ed. In: Immunology and Allergy Clinics of North America 1995;15: 761–774.
7. Aboobaker J, Greaves MW. Urticarial vasculitis. Clin Exp Dermatol 1986;11:436–444.
8. McDuffie FC, Sams WM Jr, Maldano JE. Hypocomplementemia with cutaneous vasculitis and arthritis: possible immune complex syndrome. Mayo Clin Proc 1973;48:340–348.
9. Soter NA. Chronic urticaria as a manifestation of necrotizing venulitis. N Engl J Med 1977;296:1440–1442.
10. Sher T. Generalized pruritis in a 62 year old male. Ann Allergy 1990;64: 422–425.
11. Millar MM, Patterson R. A patient referred for evaluation of angioedema. Ann Allergy Asthma Immunol 1998;81:120–126.
12. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. JAMA 1997;278:232–233.
13. Sussman GL, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. 1991;265: 2844–2847.
14. Valentine MD. Allergy to stinging insects. Ann Allergy 1993;70:427–432.
15. Valentine MD. Insect venom allergy: diagnosis and treatment. J Allergy Clin Immunol 1984;73:299–304.
16. Wanderer AA. The spectrum of cold urticaria. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15:701–723.
17. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. J Allergy Clin Immunol 1980;66:106.
18. Volcheck GW, Li JTC. Exercise-induced urticaria and anaphylaxis. Mayo Clin Proc 1997;72:140–147.
19. Dover J, Black A, Ward A. Delayed pressure urticaria: clinical features, laboratory investigations and response to therapy of 44 patients. J Am Acad Dermatol 1988;18: 1289–1298.
20. Rance F, Kann G, Dutau G, Moneret-Vautrin DA. Food hypersensitivity in children: clinical aspects and distribution of allergens. Pediatr Allergy Immunol 1999;10:33–38.
21. Jarisch R, Beringer K, Hemer W. Role of food allergy and food intolerance in recurrent urticaria. Curr Prob Dermatol 199;28:64–73.
22. Castillo R, Delgado J, Quiralte J et al. Food hypersensitivity among adult patients: epidemiological and clinical aspects. Allergol Immunopathol 1996;24:93–97.
23. Lehach JG, Rosenstreich DL. Clinical aspects of chronic urticaria. 1992; 10:281–301.
24. Kaplan AP. Urticaria and angioedema. In: Middleton E, Reed CE, Ellis EF, et al, eds. Allergy, principles and 5th edition 1998;1113–1114.
25. Hara T, Shiotani A, Matsunaka H, et al. Hereditary angioedema with gastrointestinal involvement: endoscopic appearance. Endoscopy 1999;31: 322–324.
26. Shah TJ, Knowles WO, McGready SJ. Hereditary angioedema with recurrent abdominal pain and ascites. J Allergy Clin Immunol 1995;96: 259–261.
27. Cicardi M, Agostoni A. Hereditary angioedema. N Engl J Med 1996;334: 1630–1634.
28. Zahedi R, Aulak KS, Eldering E, Davis AE. Characterization of C1 inhibitor-Ta. A dysfunctional C1INH with deletion of lysine 251. J Biol Chem 1996;271:24307–24312.
29. Cicardi M, Bergamaschini L, Cugno M, et al. Pathogenetic and clinical aspects of C1 inhibitor deficiency. Immunobiology 1998;199:366–376.
30. Valsecchi R, Reseghetti A, Pansera B, Di Landro A. Autoimmune C1 inhibitor deficiency and angioedema. Dermatology 1997;195:169–172.
31. Donaldson VH, Bernstein DI, Wagner CJ, et al. Angioneurotic edema with acquired C1 inhibitor deficiency and autoantibody to C1 inhibitor: response to plasmapheresis and cytotoxic therapy. J Lab Clin Med 1992; 119:397–406.
32. Norsworthy P, Theodorides E, Botto M, et al. Overrepresentation of the Fcgamma receptor type IIA R131/R131 genotype in caucasoid SLE patients with autoantibodies to C1q and glomerulonephritis. Arthritis Rheum 1999;42:1828–1832.
33. Walport MJ, Davies KA, Botto M. C1q and SLE. Immunobiology. 1998;

199:265–285.
34. Hasely LA, Wisnieski JJ, Denburg MR, et al. Antibodies to C1q in SLE: characteristics and relation to Fegamma RIIA alleles. Kidney Int 1997;52:1375–1380.
35. Drug hypersensitivity: a practice parameter. Ann Allergy Asthma Immunol 1999;83:S665–S700.
36. Nicklas RA, Bernstein IL, Li JT, Lee RE, et al. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101:S465–S528.
37. Lieberman A. The use of fresh-frozen plasma in hereditary angioedema. JAMA 1994;272:518.
38. Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion; 1998;38:540–549.
39. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med 1976;84:580.
40. Greaves M, Lawlor F. Angioedema: manifestations and management. J Am Acad Dermatol 1991;25: 155–161.
41. Vaughn MP, DeWalt AC, Diaz JD. Urticaria associated with systemic disease and psychological factors. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15:725–740.
42. Berg RE, Kantor GR, Bergfeld WF. Urticarial vasculitis in adults. Int J Dermatol 1988;27:504–505.
43. Sanchez NP, Winkelmann RK, Schroeter AL, et al. The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. J Am Acad Dermatol 1982;7: 599–605.
44. Stack PS. Methotrexate for urticarial vasculitis. Ann Allergy 1994;72: 36–38.
45. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol 1992;26: 441–448.
46. Champion RH. Urticaria and angioedema: a review of 554 patients. Br J Dermatol 1969;81:588–597.
47. Huston DP, Bressler RB. Urticaria and angioedema. Med Clin North Am 1992;76:805–840.
48. Schafer CM. Physical urticaria. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15:679–699.
49. Stafford CT. Urticaria as a sign of systemic disease. Ann Allergy 1990; 64:264–270.
50. Ostrov MR: Dramatic resolution of chronic urticaria. Ann Allergy Asthma Immunol 1995;75:227–231.
51. Gruber BL, Baeza ML, Marchese MJ, et al. Autoantibodies in urticarial syndromes. J Invest Dermatol 1988;90: 213–217.
52. Hide M, Francis DM, Gratten CE, Hakimi J. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328: 1599–1604.
53. Farah FS, Shbaklu A. Autoimmune progesterone urticaria. J Allergy Clin Immunol 1997;48:257–261.
54. Mittman RJ, Bernstein DI, Steinberg DR, et al. Progesterone-responsive urticaria and eosinophilia. J Allergy Clin Immunol 1989;84:304–310.
55. Bernstein IL, Martin RLM, Lumus ZL, et al. Both immune and nonimmune reactions to progesterone (P) occur in women with cyclic hives/ angioedema/anaphylaxis [Abstract]. J Allergy Clin Immunol 1999;103: S152.
56. Massod D, Brown JE, Patterson R, et al. Recurrent anaphylaxis due to unrecognized latex hypersensitivity in two healthcare professionals. Ann Allergy Asthma Immunol 1995;74: 311–313.
57. Mathias CGT. Contact urticaria from peanut butter. Contact Dermatitis 1983;9:66.
58. Maibach HI, Johnson HL. Contact urticaria syndrome: contact urticaria to diethyltoluamide (immediate hypersensitivity). Arch Dermatol 1975; 111:726.
59. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol 1989;84:66–71.
60. Rumbyrt JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. J Allergy Clin Immunol 1995;96: 901–905.
61. Turktas I, Gokcora, Demirsoy S, et al. The association of chronic urticaria and angioedema with autoimmune thyroiditis. Int J Dermatol 1997;36:187–190.
62. Moore-Robinson M, Warin RP. Effect of salicylates in urticaria. Br J Med 1967;4:262.
63. Warin RP. The effect of aspirin in chronic urticaria. Br J Med 1960;72: 350.
64. Kaplan AP. Chronic urticaria. Possible causes, suggested treatment alternatives. Postgrad Med 1983;74: 209–215.
65. Orfan N, Kolski G. Physical urticarias. Ann Allergy 1993;71:205–212.
66. Sussman G, Harver R, Schocket A. Delayed pressure urticaria. J Allergy Clin Immunol 1982;70:337–342.
67. Engler R, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. Ann Allergy Asthma Immunol 1995;74:155–159.
68. Briner WW, Bruno PJ. Case report: 30 year old female with exercise-induced anaphylaxis. Med Sci Sports Exerc 1991;23:991–994.
69. Kidd J, Cohen S, Sosman A. Food-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol 1983; 71:407–411.
70. Suko M, Dohi M, Sugeyama H, et al. Three cases of food-dependent exercise induced anaphylaxis in which aspirin exacerbated symptoms. Arregugi 1990;39:1598.
71. Sheffer A, Austen K. Exercise-induced anaphylaxis. J Allergy Clin Immunol 1984;73:699–703.
72. Garafalo J, Kaplan A. Histamine release and therapy of severe dermatographism. J Allergy Clin Immunol 1981;68:103–105.
73. Balfour HH: Antiviral drugs. N Engl J Med 1999;340:1255–1268.
74. Kennard CD. Evaluation and treatment of urticaria. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15: 785–801.
75. Charlesworth EN, Massey WA, Kagey-Sobotka A, et al. Effect of H_1 receptor blockade on the early and late response to cutaneous allergen challenge. J Pharm Exp Ther 1992; 262:964–970.
76. O'Hanlon JF. Antihistamine effects on actual driving performance in a standard test. A summary of the Dutch experience, 1989–1994. Allergy 1995;50:234–242.
77. Gengo FM, Manning C. A review of the effects of antihistamines on mental processes related to automobile

driving. J Allergy Clin Immunol 1990;186:1034–1039.
78. Adelsberg BR, D'Amico-Beadone A. The effects of loratadine, diphenhydramine and placebo on worker productivity. Results of a double blind trial. J Allergy Clin Immunol 1990; 85:296.
79. Vuurman EFPM, van Veggel LMA, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993;71:121–126.
80. Kay GG et al. Self-reported sedation doesn't predict impaired CNS functioning after dose of sedating antihistamine. J Allergy Clin Immunol 1999;103: (1 pt 2):S254.
81. Simons FER. The antiallergic effects of antihistamines (H_1-receptor antagonists). J Allergy Clin Immunol 1992;90:705–715.
82. Baroody FM, Lim MC, Proud D, et al. Effects of loratadine and terfenadine on the induced nasal allergic reaction. Arch Otolaryngol Head Neck Surg 1996;122:309–316.
83. Heymann WR. Chronic Urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. J Am Acad Dermatol 1999;40:229–232.
84. Rawnsley HM, Shelley WB. Cold urticaria with cryoglobulinemia in a patient with chronic lymphocytic leukemia. Arch Dermatol 1968;98:12–17.
85. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to food in asthmatic children. J Allergy Clin Immunol 1976;58:500–515.
86. Sampson HA. Adverse reactions to foods. In: Middleton E, Reed CE, Ellis EF, eds. Allergy, principles and practice 5th edition 1998:1162–1182.
87. Greaves MW, O'Donnell BF. Not all chronic urticaria is idiopathic. Exp Dermatol 1998;7:11–13.
88. Jones RR, Bhogal B. Urticaria and vasculitis. Br J Derm 1983;108:695.
89. Gratten CEH, Boon AP, Winkelmann RK. The pathology of autologous serum skin test response in chronic urticaria resembles IgE-mediated late phase reactions. Int Arch Allergy Appl Immunol 1990;93:198–204.
90. Toppe E, Haas N, Heng BM. Neutrophilic urticaria: clinical features, histological changes and possible mechanisms. Br J Dermatol 1998;138: 248–253.
91. Sabroe RA, Poon E, Orchard GE, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-$Fc_\epsilon RI$ or anti-IgE autoantibodies. J Allergy Clin Immunol 1999; 103:484–493.
92. DiBacco RS, DeLeo VA. Mastocytosis and the mast cell. J Am Acad Dermatol 1982;7:709–722.
93. Tharp MD. The spectrum of mastocytosis. Am J Med Sci 1985;289: 119–132.
94. Goodman DL, McDonnell JT, Nelson HS, et al. Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyyanisole (BHA) and butylated hydroxytoluene (BHT). J Allergy Clin Immunol 1990;86:570–575.
95. Lindskov R, Lange Wantzin G, Knudsen L, et al. Urticaria pigmentosa treated with oral disodium cromoglycate. Dermatologica 1984;169: 49–52.
96. Welch EA, Alper JC, Bogaars H, et al. Treatment of bullous mastocytosis with disodium cromoglycate. J Am Acad Dermatol 1983;9:349–353.
97. Zavadak D, Tharp MD. Chronic urticaria as a manifestation of the late phase reaction. In: Charlesworth EN, ed. Immunology and Allergy Clinics of North America 1995;15:745–759.
98. Spector SL. Antileukotrienes in chronic urticaria [letter to the editor]. J Allergy Clin Immunol 1998:572.
99. Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. J Am Acad Dermatol 1991;25:1065–1067.
100. Tharp MD. Chronic urticaria: pathophysiology and treatment approaches. J Allergy Clin Immunol 1996;98: S325–330.
101. Grattan CEH, Francis DM, Slater NGP. Plamapheresis for severe unremitting chronic urticaria. Lancet 1992;339:1078–1080.
102. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1997;133: 1003–1008.
103. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998;138:101–106.
104. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998; 101:33–37.
105. Hiraoka E, Matsushima Y, Inomoto-Naribayashi Y, et al. Systemic capillary leak syndrome associated with multiple myeloma of IgG kappa type. Intern Med 1995;34:1220–1224.
106. Agostoni A, Cicardi M, Porreca W. Peripheral edema due to increased vascular permeability: a clinical appraisal. Int J Clin Lab Res 1992;21: 241–246.
107. Hornstein OP. Melkersson-Rosenthal syndrome—a challenge for dermatologists to participate in the field of oral medicine. J Dermatol 1997;24: 281–296.
108. Fava GA, Perini GI, Santonastaso P, et al. Life events and psychological distress in dermatological disorders: psoriasis, chronic urticaria and fungal infections. Br J Med Psychol 1980; 53:277.
109. Sperber J, Shaw J, Bruce S. Psychological components and the role of adjunct interventions in chronic idiopathic urticaria. Psychother Psychosom 1989;51:135.
110. Schwartz LB, Yunginger JW, Miller, et al. The time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. J Clin Invest 1989;83: 1551–1555.
111. Hogan AD, Schwartz LB. Markers of mast cell degranulation. Methods 1997;13(1):43–52.
112. Callen JP, Kalbfleisch S. Urticarial vasculitis: a report of nine cases and review of the literature. Br J Dermatol 1982;107:87–94.
113. Matteson EL. Interferon alpha 2a therapy for urticarial vasculitis with angioedema apparently following hepatitis A infection. J Rheumatol 1996;23:382–384.
114. Koehn GG, Thorne EG. Urticaria and viral hepatitis. Arch Dermatol 1972; 106:422.
115. Reichel M, Mauro TM. Urticaria and hepatitis C. Lancet;1990;336:822.
116. Adkinson NF. Drug allergy. In: Middleton E, Reed CE, Ellis EF, eds. Allergy, principles and practice, 5th ed. 1998:1212–1224.
117. Shelley W, Rawnsley H. Aquagenic urticaria. JAMA 1964;189:895–898.
118. Lemanske RF, Bush RK. Cold urticaria in infectious mononucleosis. JAMA 1982;247:1604.
119. Wu LYF, Mesko JW, Petersen BH.

Cold urticaria with infectious mononucleosis. Ann Allergy 1983;50: 271–274.
120. Platts-Mills TA, Fiocco GP, et al. Serum IgE antibodies to Trichophyton in patients with urticaria, angioedema, asthma, and rhinitis: development of a RAST. J Allergy Clin Immunol 1987;79:40.
121. Holmes RC, Black MM. The specific dermatoses of pregnancy. J Am Acad Dermat 1983;8:405.
122. DeShazo RD, Banks WA. Medical consequences of multiple fire ant stings occurring indoors. J Allergy Clin Immunol 1994;93:847–850.
123. Reisman RE. Unusual reactions to insect venom. Allergy Proc 1991;12: 395–399.
124. Reisman RE, Livingston A. Late-onset allergic reactions, including serum sickness, after insect stings. J Allergy Clin Immunol 1989; 331–337.
125. Harvell J, Bason M, Maibach H. Contact urticaria (immediate reaction syndrome). Clin Rev Allergy 1992; 10:303–323.
126. Torresani C, Periti I, Beski L. Contact urticaria syndrome from formaldehyde with multiple physical urticarias. Contact Dermatitis 1996;35: 174–175.
127. Muckle TJ, Wells M. Urticaria, deafness and aneyloidosis: a new heredofamilial syndrome. Quart J Med 1962;31:235.
128. Armstrong JL, Stafford CT. Chronic idiopathic urticaria: a satisfactory outcome. Ann Allergy Asthma Immunol 1999;83:95–98.
129. Leichty RD, Firminger HI. Hyperparathyroidism and urticaria. JAMA 1983;250:789–790.
130. Ormerod AD, Reid TM, Main RA. Penicillin in milk–its importance in urticaria. Clin Allergy 1987;17: 229–234.
131. Krainock RJ. Prolonged milk residue in two cows after subcutaneous injections of penicillin at an extra-label dose. J Am Vet Med Assoc 1991;198: 862–863.
132. Dewdney JM, Edwards RG. Penicillin hypersensitivity–is milk a significant hazard? a review. J Royal Soc Med 1984;77:866–877.
133. Bernstein IL, Storms, WW. Practice parameters for allergy diagnostic testing Ann Allergy Asthma Immunol 1995;75:543–625.
134. Katsarou A, Armenaka M, Ale I, et al. Frequency of immediate reactions to the European Standard Series. Contact Dermatitis. 1999;41: 276–279.
135. Katsarou A, Armenaka M, Kalogeromitros D, et al. Contact dermatitis to fragrance. Ann Allergy 1999;82: 449–455.
136. Wilkinson SM, Burd R. Latex: a cause of allergic contact eczema in users of natural rubber gloves. J Am Acad Dermatol 1998;39:36–42.
137. Jeannet-Peter N, Pilettat-Zanin PA, Hauser C. Facial dermatitis, contact dermatitis, rhinoconjunctivitis, and asthma induced by potato. Am J Contact Dermatitis 1999;10: 40–42.
138. Kanerva L, Estlander T. Immediate and delayed skin allergy from cow dander. Am J Contact Dermat 1997; 8:167–169.
139. Taylor JS, Praditsurvan P. Latex allergy: review of 44 cases including outcome and frequent association with allergic hand eczema. Arch Dermatol 1996;132:265–271.

CONSUMER HABITS AND PRACTICES STUDY PROTOCOL OUTLINE AND SUMMARY OF FINDINGS

BACKGROUND AND OBJECTIVES

In order to better understand chronic idiopathic urticaria and the consumer habits and practices among those patients who suffer it, Schering-Plough commissioned a survey research study.

Specifically, the objectives of this research were:

- To understand, from a patient perspective, fundamental dynamics such as frequency of suffering, symptoms suffered and duration, severity and bothersomeness of the condition.
- Patient interaction with their physician initially, when diagnosed as idiopathic and when their condition worsens or does not respond to traditional treatment.
- Treatment modalities and preparations used to manage the disorder.
- Ease of recognizing the condition once a diagnosis of chronic idiopathic urticaria has been rendered by a physician.

STUDY DESIGN AND PROCEDURES

A survey was conducted using the National Family Opinion Interactive Panel of 1.2 million U.S. households. Given the low incidence of chronic idiopathic urticaria (CIU) in the population, an omnibus research tool was used to identify a sufferer population. Over two consecutive weeks (10/30/01 and 11/6/01) surveys were e-mailed to over 500,000 households each week. Each omnibus survey resulted in approximately 15,000 qualified adult subjects. The reported incidence of CIU ranged from 2.7% in Week One to 3.3% in the Week Two. To qualify as a sufferer, respondents were required to answer the following question in the affirmative:

"*Have you ever been diagnosed by a medical doctor as having chronic or recurrent hives that have no known discernible cause (also known as chronic urticaria)?"*

Upon completion of the omnibus surveys, a more detailed interactive survey was fielded among a sub-sample of subjects randomly drawn from the larger pool of 15,000. The size of the sub-sample was derived with the goal of achieving an ending sample size of 300 chronic idiopathic urticaria sufferers and a projected response rate among the panel of 35%.

The more detailed survey was fielded on 11/9/2001 and completed on 11/14/2001. A total of 388 panelists completed the survey. The only remuneration that panelists who completed the survey received was a nominal number of points to thank them for participating. These points can be accumulated and redeemed by panelists for gifts.

Survey questions were a combination of closed-and open-ended questions. Closed-ended questions were answered via buttons or click boxes. Many of the closed-ended questions had an "Other – Specify" response which permitted study subjects to type a response other that those in the pre-set lists into their browser. Responses to open-ended questions were typed directly into a response area on the study participant's screen. For a number of the "list" questions (e.g., symptoms, descriptors) the list elements were programmed to be rotated randomly.
In the case of this study, the universe of sufferers was primarily a self-defined group due to the low single-digit incidence and therefore extensive weighting was not appropriate.

Although internet access is not yet ubiquitous (just under 60% of the U.S. population has access to the internet) and internet samples somewhat under represent non-whites, the NFO WorldGroup In-Depth Interactive Panel permitted many benefits. These include:

- Comparison to a parallel internet survey conducted among physicians without having to account for methodological differences
- Precise targeting of the hard-to-identify, low incidence CIU population
- A solution to the declining response rates of telephone surveys due to proliferation of caller ID and telephone answering machines and to the socio-economic skews of mall intercept samples
- Avoidance of interviewer bias or translation errors since subjects enter responses directly into their browsers
- Less burden on respondents since subjects could take the survey at their convenience rather than a prescribed time (e.g., the dreaded dinner hour call). This has the additional benefit of reaching respondents not normally available during standard interviewing periods.

DATA PROCESSING AND ANALYSIS

All questionnaires were electronically downloaded by National Family Opinion Interactive. Each questionnaire was checked for completeness and accuracy. Where necessary, verbatim responses were reviewed and classified into appropriate codes. All codes and component responses were reviewed and confirmed by National Family Opinion Interactive. Statistical testing was conducted and noted on the data tables. Significance testing was undertaken at the 95% confidence level using a two-tailed test.

SUMMARY OF FINDINGS

- These results show that CIU is a bothersome condition among those who experience it with over seven in ten subjects (73%) rating it extremely or very bothersome. Interestingly, these same subjects do not see the condition as severe with only 4% of sufferers viewing the condition as extremely serious.
- Those who have recurrent episodes of CIU are experienced, frequent sufferers. The ailment is frequently suffered with over 40% of subjects experiencing five or more outbreaks each year and one in six experiencing constant episodes.
- There is significant consistency in the symptoms described by CIU sufferers with 91% naming itching as the dominant symptom. Hives or wheals (77%), redness (68%) and rash (50%) also receive high levels of mentions as key symptoms. Conversely, the reported incidence of symptoms that could connote or be confused with anaphylaxis or angioedema is very low (swelling = 4%; breathing problems = 1%).
- One third of sufferers claim to have not seen a physician in the past year for their chronic hives and nearly 20% of study subjects have not seen a physician since initial diagnosis.
- The behavior of not contacting the physician at every outbreak appears to be due, in part, to the use of prescribed medications already on hand and the use of over-the-counter medications. Over half of study subjects (52%) indicate that they normally use a prescribed medicine already on hand when their chronic hives occur and 43% report use of OTC medications. In addition, seven in ten of those receiving prescriptions generally receive refills with their prescription and the average number of refills provided is three.
- CIU sufferers who do contact their physician when their hives recur appear to do so principally when symptoms do not respond to current treatment/medication (35%) or when more serious symptoms occur (8%). These patients do not wait long before contacting their physician with over half making contact within one day.

- Once diagnosed by a physician as having chronic idiopathic urticaria, 80% of study subjects perceive that it is very easy to identify the condition when it reappears. A total of 94% of subjects indicated that it was either very or somewhat easy. No respondent reported difficulty.
- When respondents were asked regarding what actions they would take if they experienced symptoms associated with anaphylaxis along with their hives (i.e., difficulty breathing or trouble swallowing), 95% of subjects indicated they would seek emergency care or call/visit their physician.
- Prior to seeing a physician for their initial outbreak, about two-thirds of study subjects (62%) indicated that they took an over-the-counter antihistamine for their hives. Continued itching/discomfort (62%), hives that would not go away (46%) and the desire to find a cause of the hives (57%) were all key motivators for the initial physician visit.
- Just under one quarter of study subjects indicate that the physician who diagnosed them with CIU recommended an over-the-counter medication, despite lack of indication approval and appropriate labeling guidelines and precautions.

CONCLUSIONS

Once diagnosed by a physician as having chronic idiopathic urticaria (CIU), sufferers appear confident in their ability to recognize a recurrent episode of the condition.

This ability traces to a number of important characteristics. First, symptoms of CIU appear to be consistent and discrete and changes in symptoms or the addition of other more troubling symptoms would seem to send signals to the consumer to seek immediate medical attention/physician contact. Also, the frequency of occurrence provides an experience base with the condition for most diagnosed sufferers that lead them to understand the natural patterns of the ailment. Finally, although they see the condition as quite bothersome, a majority of sufferers do not perceive the condition as serious or severe.

CONCLUSIONS (continued**)**

Behavior already appears to exist among consumers for self-treatment of the condition with antihistamines. A sizeable proportion of sufferers have not seen a physician for CIU since diagnosis. Additionally, consumers often use over-the-counter antihistamines prior to seeking a diagnosis, and after diagnosis, many consumers use OTC medications on the recommendation of their physician. Based on the proportion of CIU patients reporting they receive refills and the number of refills, many physicians appear to encourage self-management, prescribing medications in advance of outbreaks.

DIALOG Accession Number: 02257569 Supplier Number: 921201061
Cold, Cough, Allergy, Bronochodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antihistamine Drug Products
Volume: 57 Issue: 237 Page: 58356
CITATION NUMBER: 57 FR 58356
Date: WEDNESDAY, DECEMBER 9, 1992

AGENCY: Department of Health and Human Services--(HHS); Public Health Service--(PHS); Food and Drug Administration--(FDA); Center for Drug Evaluation and Research--(CDER)
DOCUMENT TYPE: Rules and Regulations
CFR: 21 CFR Part 210 310 341 369
NUMBERS: No. 76N-052H; RIN 0905-AA06
DATES: Effective: 19931209
CONTACT INFORMATION: William E. Gilbertson, 301-295-8000
ACTION: Final rule
INTERNAL DATA: (FR Doc. 92-29718 Filed 12-8-92; 8:45 am)
Word Count: 19687

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis)) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on antihistamine drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC antihistamine ingredients that have been found to be not generally recognized as safe and effective or are misbranded and were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

TEXT:
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
21 CFR Parts 201, 310, 341, and 369
(Docket No. 76N-052H)
RIN 0905-AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Antihistamine Drug Products

AGENCY: Food and Drug Administration, HHS.
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antihistamine drug products (drug products used for the relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis)) are generally recognized as safe and effective and notmisbranded.
FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on antihistamine drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC antihistamine ingredients that have been found to be not generally recognized as safe and effective or are misbranded and were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: December 9, 1993.

25. Two comments requested that the agency include the symptomatic treatment of allergic itching as a monograph condition in the final monograph for OTC antihistamine drug products. One comment requested this indication specifically for oral diphenhydramine, while the other comment requested the indication for all orally administered OTC antihistamines

The comment that requested monograph status for oral diphenhydramine requested the following indication: "For temporary relief of itching associated with hives, minor skin irritations, or rashes due to food or animal allergies, insect bites, inhaled allergens (dust, mold, spores), poison ivy, oak, or sumac, soaps, detergents, cosmetics, and jewelry." The comment contended that the proposed indication involves only symptoms which consumers can recognize and treat, and that the indication is currently approved for prescription dispensing of diphenhydramine hydrochloride at the dose already accepted for OTC marketing. This comment was subsequently withdrawn, but no reasons were given (Ref. 1).

The second comment cited statements from three references to support the effectiveness of orally administered antihistamines for the relief of pruritus, angioedema, and other manifestations of skin allergies: (1) prior administration of chlorpheniramine raised the itch thresholds to both 2- methyl histamine and histamine itself (Ref. 2), (2) traditional antihistamines of the H1 type are the mainstay in the management of urticaria (Ref. 3), and (3) certain of the allergic dermatoses respond favorably to H1 blockers; H1 blockers also have a place in the treatment of itching pruritides; and some relief may be obtained in many patients suffering atopic dermatitis and contact dermatitis, although topical corticosteroids seem to be more valuable in such diverse conditions as insect bites and ivy poisonings (Ref. 4). The comment requested that the indications in Sec. 341.72(b) be expanded to permit the following claim: "* * * or the itching skin caused by allergy to local irritants such as poison ivy, oak, or sumac, or caused by hives."

The agency has reviewed the information provided by the comment and determined that it is insufficient to support general recognition of the symptomatic treatment of allergic itching as an appropriate OTC indication for oral antihistamine drug products. Hives and pruritic rashes secondary to foods, animal allergies, and insect stings and bites can be one component of a systemic anaphylactic reaction, and the use of an OTC antihistamine could potentially delay more appropriate treatment that may be needed. The agency is unaware of any data demonstrating that the average person can distinguish between a mild allergic reaction and a life-threatening reaction that may begin with itching only. Histamine is only one of the mediators released during mast cell degranulation (Ref. 5). Therefore, the use of an antihistamine alone may not be sufficient.

The agency does not find that the references cited by the comment support OTC use of oral antihistamines for pruritus, angioedema, and other manifestations of skin allergies. For example, Monroe (Ref. 3) also said that the ideal treatment for urticaria is identification and removal of its cause and that oral antihistamines of the H1 type are the usual medical treatment for acute urticaria, but medical management is required in severe urticarial reactions. Further, the edition of Goodman and Gilman cited by the comment included in its discussion of allergic dermatoses the caveat that, although angioedema is responsive to treatment with antihistamines, the paramount importance of epinephrine in the severe attack must be emphasized (Ref. 4). This caution is carried through to the current edition of Goodman and Gilman as well (Ref. 5). Poison ivy, oak, and sumac are examples of contact dermatitis. The Merck Manual (Ref. 6) states that, although an oral corticosteroid should be given in severe cases and the treatment for contact dermatitis is usually topical corticosteroids, antihistamines are ineffective in cases of contact dermatitis except for their sedative effect.

Based upon currently available data, the agency concludes that there is a lack of information to support an OTC indication for allergic itching related to hives and rashes. Thus, the use of OTC oral antihistamines for self- treatment of these problems remains a nonmonograph condition at this time.

References

(1) Comment No. WDL 1, Docket No. 76N- 052H, Dockets Management Branch.

(2) Davies, M. G., and M. W. Greaves, "The Current Status of Histamine Receptors in Human Skin: Therapeutic Implications," British Journal of Dermatology, 104:601-606, 1981.

(3) Monroe, E. W., "Treatment of Urticaria," Dermatologic Clinics, 3:51-55, 1985.

(4) Douglas, W. W., "Histamine and 5-Hydroxytryptamine (Serotonin) and Their Antagonists," in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 6th Ed., edited by A. G. Gilman, L. S. Goodman, and A. Gilman, Macmillan Publishing Co., New York, pp 622-646, 1980.

(5) Garrison, J. C., and T. W. Rall, "Histamine, Bradykinin, 5-Hydroxytryptamine, and Their Antagonists,"in "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 8th Ed., edited by A. G. Gilman, et al., Pergamon Press, New York, pp. 574-588.

(6) Berkow, R., editor, "The Merck Manual," 15th Ed., Merck & Co., Inc., Rahway, NJ, pp. 2255-2257, 1987.

PHYSICIANS PRACTICES STUDY PROTOCOL OUTLINE AND SUMMARY OF FINDINGS

BACKGROUND AND STUDY OBJECTIVES

The purpose of this survey research study was to quantitatively explore the current habits and practices of physicians surrounding the diagnosis and treatment of patients with Chronic Idiopathic Urticaria (CIU).

Specifically, the objectives of this research were:

- To understand a treating physician's diagnostic procedures as well as their perspective toward the fundamental dynamics of CIU such as symptoms that present, frequency and duration of episodes.
- To determine physicians' perceptions regarding a patient's ability to recognize an episode of chronic idiopathic urticaria prior to and after receiving a diagnosis.
- To understand the physician's view of patient self-management practices following diagnosis and recommended treatment regimens.

STUDY DESIGN

A total of 359 qualified interviews among medical doctors were completed among an Internet panel of physicians. The sample included several medical specialties reflecting the primary treating groups as determined by IMS, a national prescription tracking research service. The relative sample size of each sub-group was determined by the proportion of treating physicians within IMS.

To be representative of the treating physician population, a sample size of a minimum of 325-350 physicians was desired. 359 interviews were completed. This sample size delivers a standard error of ± 5.2%. The sub-group sample sizes follow.

- 151 Primary Care Physicians (PCP's)[1]
- 75 Dermatologists
- 55 Allergists
- 78 Pediatricians

The study was conducted by Market Measures, Inc. (MMI). Physicians were randomly selected from MMI's nationally representative e-panel and web site membership databases. MMI has broad access to physicians through a variety of channels. Their own panel, the Medical Marketing Conference (MMC), provided the primary resource for this study. The MMC panel contains 22,000 physicians representing 56 medical specialties. The MMC panel is representative of the universe of physicians on two variables: age and region of the country. Added to the MMC panel is access via an alliance with Medscape. Medscape is among the top five visited physician websites on the Internet.

STUDY PROCEDURES

Physicians were prescreened for this study. Once specialty was determined, physicians were identified as treating patients with CIU. The criterion for inclusion was treating a minimum of one patient, on average, per month for CIU. No exclusion criteria were employed.

Once screened, a detailed survey was conducted among qualifying physicians. The survey instrument was self-administered and responses were electronically submitted via the Internet.

The questions were a combination of closed- and open-ended questions. Closed-ended questions were answered via buttons or click boxes. Responses to open-ended questions were typed directly into a response box on the study participant's screen.

---

[1] PCP's were defined as Family Practitioners/General Practitioners (n=75) or Doctors of Internal Medicine (n=75)

DATA PROCESSING AND ANALYSIS

All questionnaires were electronically returned to MMI. Each questionnaire was checked for completeness and accuracy. All verbatim responses were reviewed and classified into appropriate codes. All codes and component responses were reviewed and verified by MMI.

All statistical testing was then conducted and noted on the data tables. Significance testing within the tables was conducted at 95% confidence level using a two-tailed test.

SUMMARY OF FINDINGS

- On average, and across the specialties represented, physicians responding to the survey see/treat 15 patients with urticaria in an average month. Over one third of these (6 patients) experience chronic idiopathic urticaria.
- Physician experience confirms that patients suffer relatively frequently. Over half (55%) of physicians observe episode duration of 7 weeks or longer and 45% indicate that their CIU patients experience between 2 and 5 episodes per year.
- The vast majority of professionals surveyed (96%) feel that it is either very or somewhat likely that once a patient has been diagnosed by a physician as having CIU, the patient is able to recognize a recurrent episode. These same physicians feel less confident about a patient being able to recognize an episode prior to diagnosis (36% very/somewhat likely).
- More than 80% of study physicians recommend that half or more of their previously diagnosed CIU patients have a prescription or OTC medication on hand in case of recurrent episodes.
- The primary symptoms associated by physicians with their CIU patients are confined to a relatively “short list” (itching=94%; Erythema=83%; Rash=81%;

Presence of wheals=79%). This focused list of symptoms perhaps contributes to the perceived ease of recognition by patients upon recurrence.

- When a previously diagnosed CIU patient contacts the physician's office, a majority (67%) make an appointment for an office visit. The remaining one-third requests a phone conference. Among those requesting a phone conference regarding a recurrent episode, 82% are phoned in a prescription.
- Prescription and OTC medications are both regularly used to treat CIU. 94% of physicians interviewed prescribe Rx antihistamines. Second generation antihistamines are prescribed to treat CIU by 88% of physicians.
- Nearly half of study physicians (48%) recommend OTC's, generally as part of combination therapy. The proportion of study physicians using OTC's as monotherapy is lower (15%).

CONCLUSIONS

Based on the results of this research, physicians who treat patients with chronic idiopathic urticaria have a high level of confidence (96%) that a previously diagnosed patient is able to self-identify recurring episodes of the condition. The ability to self-identify or recognize CIU is also most likely strengthened by the visible and easily recognizable symptomology that presents with CIU (e.g., wheals and intense itching).

The results from this research also demonstrate physicians feel that recurrent episodes of this condition are self-treatable among those patients who have been previously diagnosed with CIU. Once diagnosed, there is a high level of patient independence surrounding treatment of recurrent cases of chronic idiopathic urticaria. More than half (58%) of physicians interviewed recommend that all of their diagnosed CIU patients keep prescription or over-the-counter (OTC) medication on hand in anticipation of treating a recurrent episode of CIU. When previously diagnosed patients contact their physician by phone for consultation regarding a CIU episode, 82% of physicians prescribe/phone-in prescriptions for treatment.

94% of physicians interviewed prescribe Rx antihistamines. OTC medications play an important and common role in treatment of CIU. Nearly half (48%) of physicians interviewed recommend OTC's generally as part of combination therapy. It is noteworthy that OTC antihistamines are recommended for the treatment of CIU despite the lack of package labeling for this indication.


CLARITIN*
10 mg de loratadine
Démangeaisons de la peau
SANS SOMNOLENCE
Soulagement rapide des réactions allergiques cutanées :
démangeaisons de la peau
urticaire
24 heures
10 COMPRIMÉS
DIN 00782696
561
CLARITIN is a fast and long-acting antihistamine which provides relief of allergic skin conditions and helps stop sneezing, runny nose and watery eyes without causing drowsiness. CAUTION: If you are pregnant, nursing a baby, or have liver disease, seek the advice of a physician before using this product. Product monograph available to health professionals upon request. Keep this and all medication stored in a safe place and out of reach of children.
Store between 2° and 30°C and protect from exposure to excessive moisture.
10
71-120414
ALLERGY INFORMATION?
RENSEIGNEMENTS SUR LES ALLERGIES?
1 800 665-1507
http://www.claritin-cdn.com
Made in Canada/Fabriqué au Canada
* Reg. T.M./Marque déposée, Schering Canada Inc., Pointe-Claire, Québec H9R 1B4
loratadine 10 mg
CLARITIN*
NON-DROWSY
Skin Itch
24 hour
Fast relief from allergic skin conditions:
Skin Itch
Hives
10 TABLETS
DIN 00782696
COMPOSITION: Each tablet contains loratadine 10 mg. DOSAGE: Adults and children over 12 years of age: 1 tablet once daily. Do not exceed the recommended dosage. Prolonged usage should only be on the advice of a physician.
NON-MEDICINAL INGREDIENTS (alphabetical order): Corn Starch, Lactose, Magnesium Stearate.
TABLETS SEALED FOR YOUR PROTECTION.
561
COMPOSITION : Chaque comprimé est dosé à 10 mg de loratadine.
POSOLOGIE : Adultes et enfants de plus de 12 ans : un comprimé une fois par jour. Ne jamais dépasser la posologie recommandée ou prolonger l'emploi sans l'avis du médecin. INGRÉDIENTS NON MEDICINAUX (ordre alphabétique) : Amidon de maïs, lactose et stéarate de magnésium.
COMPRIMÉS EN ALVÉOLES INVIOLABLES.
CLARITIN est un antihistaminique qui agit vite et pendant longtemps. Il permet de soulager les réactions allergiques cutanées et d'arrayer éternuements, écoulement nasal et larmoiement. sans provoquer de somnolence. MISE EN GARDE : Les femmes enceintes ou allaitantes et les personnes souffrant de maladies du foie doivent consulter un médecin avant de prendre ce produit. Monographie fournie sur demande aux professionnels de la santé. Conserver ce produit et tout autre médicament en lieu sûr, hors de la portée des enfants.
Conserver entre 2° et 30 °C. Protéger de tout excès d'humidité.
15
0 56219 92010 3

06UU38384CA-Q 04-11-1999 16:30 Pagina 1

MBC2 (34707)

PM3 06UU38384CA

pms 362 green pms 116 yellow pms 280 blue pms 032 red pms Clarityn Cyan black

06UU23705IN 23-01-2001 10:51 Pagina 1

CLARITYN® Allergy tablets

Loratadine

06UU23705INR

Patient Information Leaflet

Please read this leaflet carefully
This leaflet will tell you about *Clarityn Allergy* tablets. It should give you all the information you need, but if there is anything you do not understand please ask your doctor or your pharmacist.

What is in *Clarityn Allergy* tablets?
Each tablet contains 10mg of loratadine as the active ingredient as well as the following inactive ingredients:
Hydrous lactose
Maize starch
Magnesium stearate.
There are 7 tablets in this pack.

What is the type of medicine in *Clarityn Allergy* tablets?
The medicine contained in *Clarityn Allergy* tablets is a non-sedating antihistamine. It can help relieve the symptoms of some allergies.

Who makes it?
The product licence holder is:
Schering-Plough Ltd., Shire Park, Welwyn Garden City, Herts AL7 1TW.

The manufacturer is:
Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium.

What are *Clarityn Allergy* tablets for?
In adults, *Clarityn Allergy* tablets can rapidly relieve allergy symptoms such as sneezing, runny nose and itchy, burning eyes, whether these are due to hayfever or whether they occur all year round. *Clarityn Allergy* tablets may also be taken for allergic skin conditions such as rash, itching or urticaria (hives).

Is there any reason why you shouldn't take *Clarityn Allergy* tablets?
If you have ever had an allergic reaction to *Clarityn Allergy* tablets or any of the active or inactive ingredients you should not take them.

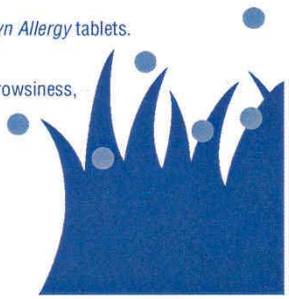
You should not take them if you are pregnant or think that you are pregnant or if you are breast-feeding.

Before taking *Clarityn Allergy* tablets
There have been no reports of undesirable effects occurring when *Clarityn Allergy* tablets have been taken at the same time as some other medicines. However, before you start taking *Clarityn Allergy* tablets, you should still tell your doctor or pharmacist if you are taking medicine for any other illness or condition.

You do not have to avoid drinking alcohol whilst taking *Clarityn Allergy* tablets.

Driving and *Clarityn Allergy* tablets
Tests have shown that *Clarityn Allergy* tablets do not cause drowsiness, so you can still drive whilst you are taking your tablets.

What is the dose?
Adults and children aged 12 years and over:
One tablet to be swallowed once daily.



PRESSPHARMA PM2 IN39V (130 x 205 mm) 06UU23705IN (recto) pms 280 blue

06UU23705IN 23-01-2001 10:51 Pagina 2

What to do if you forget to take your medicine
If you forget to take it, take your recommended dose as soon as you remember.

What you should do in the case of an overdose
If you, (or someone else) accidentally takes too many *Clarityn Allergy* tablets by mistake, you should contact your doctor immediately.

Meanwhile, try to make yourself (or the other person) vomit. Do not try to do this if you or the other person are not fully awake.

Do *Clarityn Allergy* tablets have any undesirable effects?
Most people do not have any side effects after taking *Clarityn Allergy* tablets, but as with all medicines, it may not suit everyone. The following side effects have occurred, but only rarely: Tiredness, nausea, headache, hair loss, allergic shock, effects on the liver and disturbances in heart rhythm. Also, a fast heart beat and fainting have been very rarely reported in a few people, although these may not necessarily have been caused by *Clarityn Allergy* tablets.
If you are worried by these or any other side effects, you should discuss them with your doctor or pharmacist.

Expiry date
Do not use after the date which is stamped on the pack.

Any other questions?
If there is anything about *Clarityn Allergy* tablets you do not understand or are unsure about, your doctor or pharmacist will be able to help or advise you.

Date of revision: October 2000.

SCHERING-PLOUGH CONSUMER HEALTH
DIVISION OF SCHERING-PLOUGH LTD WELWYN GARDEN CITY AL7 1TW

06UU23705INR

PRESSPHARMA PM2 IN39V (130 x 205 mm) 06UU23705IN (recto) pms 280 blue


7 Tablets
Hayfever & Allergy Relief
All Day Tablets 10mg
7 Tablets
Hayfever & Allergy Relief
All Day
Tablets 10mg
(Loratadine)
Fast acting 24 hour relief. Non-drowsy.
This carton is made from a minimum of 70% Recycled Fibre.
27-41-504
Hayfever & Allergy Relief
All Day Tablets 10mg
For the relief of the symptoms associated with seasonal and perennial allergic rhinitis and allergic skin conditions.
This product does not cause drowsiness and will not normally affect your ability to drive or operate machinery.
Please read enclosed leaflet before using this medication.
How to take Hayfever & Allergy Relief All Day Tablets
Check that the foil packaging is not broken before use.
Adults and Children over 12 years: One tablet once daily.
Do not take more than one tablet in any 24 hour period.
Do not give to children under 12 years.
WARNING
Do not exceed the stated dose.
If you take too many, talk to a doctor straight away.
If symptoms do not go away, talk to your pharmacist or doctor.
KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN
Active Ingredient: Each tablet contains Loratadine 10mg.
PL 0201/0175
Manufactured for The Boots Company PLC Nottingham NG2 3AA. The Product Licence holder is Schering-Plough Ltd Welwyn Garden City Hertfordshire AL7 1TW.
Do not take if pregnant or breast feeding.
Need further advice? Your pharmacist can help.
Use by:
Lot:
06JUL54290CA
MBC1
S/06471/34707
MBC 2

Hayfever & Allergy Relief
All Day Tablets

06UU56668INR

The name of your medicine is Hayfever & Allergy Relief All Day Tablets.

Each tablet contains Loratadine 10mg as the active ingredient.

Also contains: Lactose, Maize Starch, Magnesium Stearate.

Each pack contains 7 tablets.

Hayfever & Allergy Relief All Day Tablets belong to a group of medicines called antihistamines which help relieve symptoms associated with seasonal and perennial allergic rhinitis.

Manufactured for The Boots Company PLC Nottingham NG2 3AA by Schering-Plough Labo N.V. Heist-op-den-Berg Belgium The Product Licence holder is Schering-Plough Ltd Shire Park Welwyn Garden City Hertfordshire AL7 1TW.

What is your medicine for?

Hayfever & Allergy Relief All Day Tablets are for the relief of symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching and burning and itching of the eyes. They are also indicated for the relief of symptoms associated with chronic urticaria of unknown origin.

Before taking your medicine

Do not take Hayfever & Allergy Relief All Day Tablets if you are pregnant, planning to become pregnant or are breast feeding.

You must tell your pharmacist or doctor if the answer to the following question is YES.

Are you allergic to any of the ingredients shown above?

There have been no reports of undesirable effects occurring when Loratadine has been taken at the same time as some other medicines. However, before you start taking these tablets, you should tell your doctor or pharmacist if you are taking medicines for any other illness or condition.

If in doubt, talk to your pharmacist or doctor.

How to take your medicine

Check that the foil packaging is not broken before use.

Adults and Children over 12 years: One tablet once daily.

Do not take more than one tablet in any 24 hour period.

Do not give to children under 12 years.

DO NOT EXCEED THE STATED DOSE

What if you take too many?

If you take too many tablets, talk to a doctor or a hospital casualty department straight away. Take your tablets with you.

After taking your medicine

As with most medicines Hayfever & Allergy Relief All Day Tablets can sometimes cause side effects.

Tests have shown that these tablets do not cause drowsiness, however, there may be rare exceptions. Make sure that you are not affected in this way before driving or carrying out tasks requiring concentration. Rare effects reported include fatigue, nausea, headache, loss of hair, allergic reaction, abnormal heart rate, fainting and liver changes.

If concerned or anything else unusual happens, talk to your pharmacist or doctor.

If symptoms do not go away, talk to your pharmacist or doctor.

Storing your medicine

Do not take your tablets after the "Use by" date. Keep them in their original pack.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN, PREFERABLY IN A LOCKED CUPBOARD

If you have any questions or are not sure about anything, ask your pharmacist or doctor. They can obtain additional information about this medicine if necessary.

Leaflet revised June 1999.

DRAFT……. DRAFT……. DRAFT……. DRAFT ……. DRAFT…….

EXECUTIVE SUMMARY

ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CDER	Center for Drug Evaluation and Research
NDA	New Drug Application
OTC	Over-The-Counter
OPDRA	Office Of Post-Marketing Drug Assessment
QD	Once Daily
SAE	Serious Adverse Event
WR	Written Request
AERS	Adverse Event Reporting System

RESUMI

This document summarizes an extensive review of worldwide safety information related to loratadine, fexofenadine, and cetirizine that was conducted by the CDER OTC Switch Review Team in response to a Citizen Petition requesting that these drugs be switched to OTC status. The primary objective of this review was to determine whether there are safety concerns associated with loratadine, fexofenadine, or cetirizine that might preclude their appropriate use in the OTC marketplace. This review did not focus on issues related to effectiveness of these agents in the OTC setting, since there is a long history of OTC marketing of antihistamines. A summary of the safety data for each drug derived from the work-group's review is provided.

BACKGROUND

Allergic rhinitis and related conditions are generally considered amenable to self-diagnosis and self-treatment. Antihistamines as a class have a long history of OTC availability and use in these indications, with correct usage guided by "OTC monograph labeling" (21 CFR 341.72). The efficacy of this class of drug products and the appropriateness of antihistamines in general for OTC marketing is not in question. However, as with all drugs, the currently marketed OTC

antihistamines are associated with adverse effects. The most commonly reported adverse effect of currently marketed OTC antihistamines is sedation. This adverse effect is addressed as a warning in the OTC monograph and in product labeling.

The sedation that is characteristic of the older antihistamines is a well-recognized, subjectively reported, dose-related adverse effect. Cognitive and task-performance impairment are also adverse effects of these drugs, however, these effects are not as easily identified and quantified as sedation. Clinical trials demonstrating cognitive impairment on complex tasks such as simulated driving in persons receiving currently marketed OTC antihistamines are common in the peer-reviewed medical literature (see, for example, [1 - 3] and the references cited therein).

Over the past decade, newer antihistamines have been developed with a specific intent of trying to limit or eliminate sedation as an adverse effect. The antihistamines that are the subject of this safety review have been associated with fewer reports of sedation as compared to the older OTC antihistamines, and in clinical trials the frequency of sedation in patients treated with these drugs is generally only slightly in excess of that seen in patients treated with placebo. When approved in the United States, loratadine, fexofenadine, and certirizine were considered to be new molecular entities and as a precaution, pending the availability of a more extensive safety database, they were each approved as prescription-only products. This regulatory pathway has led a situation in which the antihistamines that are most associated with sedation are widely available OTC, while the antihistamines that less likely to be associated with sedation are available by prescription only.

The FDA has historically adopted a conservative approach to approval of OTC marketing for new drugs and in particular new molecular entities. A decision to approve a new drug for OTC marketing has generally been deferred until a time at which the accumulated postmarketing safety data are adequate to allow a more accurate assessment of the true safety of the drug, and to allow a more complete assessment of whether the drug can be used safely by consumers without the oversight of a physician or other caregiver. The merit of this conservative approach is exemplified by the regulatory history of two other “non-sedating” antihistamines: terfenadine (Seldane) and astemizole (Hismanal). These drugs were intitially approved in the U.S. as prescription drugs. Seldane, in particular, was later considered for OTC status. However, within the first several years of marketing of these drugs, a serious safety concern related to cardiac arrhythmias was what eventually resulted in these drugs being withdrawn from the U.S. market.

In July 1998, Dr. Robert Seidman, as a representative of Blue Cross of California, filed a Citizen Petition requesting that the Agency remove the

prescription-dispensing requirements of section 503(b)(1)(C) of the Federal Food, Drug and Cosmetic Act for three of the newer generation antihistamine single ingredient products and two combination antihistamine-decongestant products/formulations containing the active moieties loratadine, fexofenadine, and cetirizine. The drug products that are the subject of the Citizen Petition are summarized in the table below. The petitioner argued, in part, that the newer antihistamines were as safe or safer than the currently marketed OTC antihistamines and should be marketed OTC to make them more readily available to consumers. (NOTE: Not all currently approved products that contain loratadine, fexofenadine, and cetirizine are mentioned in the Citizen Petition or in the table. Other approved products include loratadine (Claritin) syrup, ceterizine (Zyrtec) syrup, loratadine (Claritin RediTabs) rapidly disintegrating tablets, and fexofenadine (Allegra) multiple strength tablets. However, these products have been included in the safety review and would be considered as part of any Agency response to the Citizen Petition.)

APPROVED FORMULATIONS CONTAINING THE ACTIVE MOIETIES LORATADINE, FEXOFENADINE, OR CETIRIZINE REFERENCED IN THE CITIZEN PETITION

Drug Product	Drug Substance and Dose	NDA	Sponsor
Allegra Capsules	Fexofenadine 60 mg	20-625	Aventis
Allegra-D Extended Release Tablets	Fexofenadine 60 mg Pseudoephedrine 120 mg	20-786	Aventis
Claritin Tablets	Loratadine 5 mg	19-658	Schering
Claritin-D 12 Hour Extended Release Tablets	Loratadine 5 mg Pseudoephedrine 120 mg	19-670	Schering
Claritin-D 24 Hour Extended Release Tablets	Loratadine 10 mg Pseudoephedrine 240 mg	20-470	Schering
Zyrtec Tablets	Cetirizine 5 mg	19-835	Pfizer

The safety review summarized in this document was conducted in response to the Citizen Petition to help the Agency to formulate an appropriate response to the actions requested by the petitioner.

REVIEW STRATEGY

The data for this review were primarily derived from three sources: the NDA safety databases for loratadine, fexofenadine, and cetirizine, the spontaneous reporting system (AERS) database, and the published literature. Information from two additional source documents, one from the Canadian drug regulatory authorities, and one from the National Transportation Safety Board (NTSB), were also incorporated into the review. In addition, public comments made at the FDA-OTC Part 15 Hearing held on June 28, 2000 (*see below*), that were relevant to this issue were also considered.

The existing NDA clinical reviews for the approved drug products were surveyed to determine whether potentially relevant information not previously described in the approved product labeling was available for any one of these three moieties. Due to a prior full review by FDA, the primary NDA data were not further re-examined. In conjunction with the fexofenadine evaluation, information regarding the closely related molecule, terfenadine, was also reviewed. Terfenadine was a pro-drug that was rapidly converted in the body to form fexofenadine, which was responsible for the majority of the effectiveness of orally administered terfenadine. While terfenadine's cardiac toxicity is widely known, a comprehensive review of terfenadine's non-cardiac adverse event profile was expected to add substantially to information available for the safety evaluation of fexofenadine.

The AERS database was extensively searched, with concentration of review efforts on AE's that appeared to be most serious or life threatening. A review of the published literature was also conducted to determine whether there were additional safety data available that were not reflected in any of the other databases reviewed.

A general review of the safety profile of the currently marketed OTC antihistamines was also undertaken. It is important to emphasize that the review of these older antihistamines was not intended to be comprehensive, or to suggest that there may be safety issues pertinent to the continued marketing of these products in this country, OTC or otherwise. Rather, the goal was to examine whether the known pharmacological properties of the earlier generation, OTC antihistamines were predictive of, and of value in identifying, potential safety issues not presently associated with the three newer products in question. The limitations of the review of the safety profile of the currently marketed OTC antihistamines are discussed at the beginning of that section.

LORATADINE

There are five approved formulations of loratadine:

NDA 19-658: Loratadine 10 mg (Claritin) tablets, approved April, 1993.
NDA 20-704: Loratadine Zydis (Claritin RediTabs), approved December, 1993.
NDA 19-670: Loratadine 5 mg/pseudoephedrine 120 mg (Claritin-D 12 Hour Extended Release tablets, approved November, 1994.
NDA 20-470: Loratadine 10 mg/pseudoephedrine 240 mg (Claritin-D 24 Hour Extended Release) tablets, approved August, 1996.
NDA 20-641: Loratadine 10 mg/10 mL (Claritin) Syrup, approved October, 1996.

The single ingredient Claritin tablet products are currently labeled for use in children age 6 years and above. Claritin Syrup was recently approved (September 26, 2000) for use in children down to age 2 years. The two Claritin-D formulations are approved for use in adults and children 12 years of age and older.

The NDA reviews for the single ingredient loratadine formulations showed that at the labeled dose of 10 mg once daily, the most commonly reported events from placebo-controlled clinical trials included headache, dry mouth, and somnolence (8% for loratadine vs. 6% for placebo vs. 22% for clemastine[4] 1 mg BID). Other safety information in the prescription package insert of potential relevance in an OTC setting include recommendations for dosing adjustment in renal failure (because of reduced loratadine clearance) and avoidance of the combination loratadine- pseudoephedrine products (Claritin-D) in patients with cardiac disease as well as hepatic insufficiency. Clinical pharmacology studies reported in the package insert and conducted in normal volunteers revealed no evidence of QT_c prolongation at doses of loratadine up to four times the labeled dose. Drug interaction studies reported in the package insert have demonstrated increased plasma loratadine and descarboethoxyloratadine[5] levels associated with coadministration of erythromycin, cimetidine, and ketoconazole. No significant effects on the QT_c interval were observed in these studies.

As of April, 2000, the AERS database contained 4081 adverse event reports in association with products containing loratadine,including 55 reports with death as an outcome. The most prevalent event categories were for “drug ineffectiveness,” “drug interaction,” “headache,” and “palpitations.” Among the serious events, three categories were identified as potential areas of concern: ventricular arrhythmias and sudden death, seizures, and hepatotoxicity. These adverse events are further evaluated below.

There were a total of 86 cases of ventricular arrhythmias, including 16 deaths, reported in association with loratadine use. Careful review of these reports by

FDA staff revealed that there were confounding factors present in the majority of cases that precluded a definitive conclusion that loratadine was causally related to the reported adverse event. These confounding factors included use of concomitant medications that might be associated with arrhythmias and pre-existing cardiovascular disease. It remains unclear whether concomitant cardiovascular disease is predictive of an arrhythmic event in association with loratadine or simply reflects the type of patient more likely to have been prescribed loratadine, given the known association of other "non-sedating" antihistamines (i.e, terfenadine and astemizole) with ventricular arrhythmias.

There were a total of 43 cases of seizures reported in association with loratadine use. Careful review of these reports by FDA staff suggested that a causal association with loratadine was possible or likely in 26 of the cases. Seizures are currently included as an adverse event in the loratadine prescription package insert. A review of the professional labeling of several currently marketed OTC antihistamines suggests that as a class, antihistamine products may rarely be associated with seizures.

Rare occurrences of liver-related events have been reported, including abnormal hepatic function, jaundice, hepatitis, and hepatic necrosis, and are currently included in the loratadine prescription package insert. In AERS, there were a total of 103 cases of hepatic injury reported in association with loratadine use. Of these, there were five cases of hepatic failure, of which four required liver transplantation. Careful review of these reports by FDA staff revealed that there were confounding factors in 3 of the 5 cases of hepatic failure that precluded a definitive conclusion that loratadine was causally related. These confounding factors included use of concomitant medications that might be associated with liver failure and recent foreign travel. To further evaluate the potential association between loratadine and hepatic failure, OPDRA reviewers undertook substantial efforts to establish a comparative background rate for occurrence of hepatic failure, which is known to occur "spontaneously" (i.e., without an identifiable cause) and which is not uncommonly reported in association with use of a wide variety of drugs. The reporting rate for hepatic failure in association with use of loratadine was several fold lower than the calculated background rate of hepatic failure (i.e., 1 per million person years). In considering these data, it is important to remember that underreporting of adverse events is a well recognized limitation of spontaneous reporting systems. Although there is no clear causal relationship between loratadine use and the occurrence of hepatic failure, the possibility that loratadine use may very rarely result in hepatic failure cannot be excluded.

Soon after approval and marketing of Claritin-D 24 Hour Extended Release Tablets in 1996, numerous reports of tablets becoming lodged in the patient's esophagus were received. Some of these cases were serious in nature and required endoscopic removal of the tablet, which had adhered tightly to the esophageal mucosa. This problem was thought to be related to the tablet coating and possibly the shape and size of the tablet. The tablet coating and

shape were changed in December 1998. No such serious adverse events have been reported for the new formulation.

A careful review of the published literature for loratadine did not provide additional insight regarding the primary areas of safety concern, nor did it identify new adverse events that were not observed in the other safety databases.

For loratadine, a report prepared by the Therapeutic Products Programme of the Bureau of Licensed Products Assessment (Canadian regulatory authorities) dated June 22, 2000 was reviewed by the FDA review team.[6] This document was prepared as part of an ongoing, comprehensive surveillance inquiry of all newer generation antihistamines presently marketed in Canada. A safety analysis of loratadine was included in this report, with the focus primarily being on cardiovascular risk. The data reviewed in the report included global safety data submitted by the drug sponsor, including all Canadian domestic as well as foreign adverse event reports, published case reports and clinical trials, and any new scientific information relevant to a benefit-risk assessment. The current marketing status of loratadine in Canada as well as internationally was also reviewed. A summary of the findings and conclusions of this report are provided below.

Loratadine was first marketed in February, 1988 in Belgium. Approval was granted in June, 1988 in Canada, where it became a non-prescription product in December, 1989. As of March, 1999, loratadine in some formulation had been approved and marketed in 94 countries worldwide, including in 17 as a non-prescription product. With the exception of the switch to non-prescription status in 1989, no significant regulatory action related to safety has been taken regarding loratadine in Canada since its approval.

The most commonly reported cardiac-related adverse events in the databases reviewed in the Canadian report were palpitations and/or tachycardia. There were cases of documented cardiac arrhythmias, although most were confounded by concomitant medications and underlying cardiac disease. The report noted that loratadine does not significantly block HERG potassium channels under the same *in vitro* conditions in which terfenadine has been shown to block these important channels that are involved in cardiac repolarization. Therefore, the authors of this report concluded that a causal association of loratadine with ventricular arrhythmias was unlikely, both from a clinical as well as a scientific standpoint.

On the other hand, new information regarding the *in vitro* affinity of loratadine for an atrial ion channel was discussed in the report. Although considered very preliminary, the possibility that a primary atrial tachycardia could be triggered under certain rare conditions was discussed as an explanation for the confirmed cases of atrial arrhythmia in the database. The authors of this report concluded that these data alone could not support a labeling change.

After careful consideration of the available data, the Canadian regulatory authorities recommended a risk management plan for loratadine. Specifically, the loratadine product monograph would be updated to include "tachycardia" under "Adverse Reactions," the adverse event databases would continue to be closely monitored by both the sponsor as well as the regulators, and the sponsor would be required to formally investigate the confounders "concomitant medications" and "underlying cardiac disease" on the cardiovascular safety of this drug product. Loratadine would remain a nonprescription product in Canada.

In conclusion, a thorough review of all available safety data for loratadine failed to identify conclusive evidence of a causal relationship between use or loratadine and serious adverse events. Potential safety signals were noted for ventricular arrhythmias and liver failure; however, as described above, the data are inconclusive and suggest that if such events were causally-related to loratadine, they are extremely unusual . A potential association between loratadine use and seizures was observed, consistent with information contained in the current package insert, and likely consistent with a class effect.

FEXOFENADINE

NDA 20-625 for Allegra capsules (fexofenadine 60 mg) was approved on July 31, 1996. Since then, two additional NDA's for drug products containing the drug substance fexofenadine have been approved, Allegra-D tablets (with the decongestant, pseudoephedrine: NDA 20-786, approved December, 1997) and Allegra multiple strength tablets (fexofenadine 30, 60, and 180 mg: NDA 20-872, approved February, 2000). Single ingredient formulations of fexofenadineare approved for use in adults and in children age 6 years and older. The combination of fexofenadine and pseudoephedrine (Allegra-D) is approved for use in adults and children 12 years of age and older.

The original reviews for these fexofenadine NDAs were assessed with respect to their safety findings. Overall, the placebo-controlled clinical trials included data from over 2000 patients age 12 years to adult. Adverse experiences occurring at a frequency of greater than >1.0% and which were more common in fexofenadine-treated patients compared to placebo included viral infection, nausea, dysmenorrhea, drowsiness (0.9% for placebo BID vs. 1.3 % for Allegra 60 mg BID), dyspepsia, and fatigue. Adverse experiences reported from Allegra-D trials reflected the contribution of the pseudoephedrine component. These adverse events noted in the preapproval clinical trials are adequately described in the "Adverse Experiences" section of the label for each of these drug products.

CONSUMER SELF-RECOGNITION AND LABEL COMPREHENSION STUDY PROTOCOL AND SUMMARY OF FINDINGS

OBJECTIVES

The objectives of this study were to evaluate how well the average consumer understood the conditions (i.e. uses, warnings and directions) in which Claritin® could be used based on his/her reading of the carton label and package insert.
In addition, this study was to determine if the subset of consumers who claimed they have been diagnosed by a physician as having recurrent hives or chronic hives of unknown origin, chronic idiopathic urticaria (CIU) could:

Accurately self-recognize the condition and symptoms upon reoccurrence.

Demonstrate comprehension of the carton label and package insert including appropriate selection for OTC Claritin® use sufficiently to self treat without physician involvement.

STUDY DESIGN

This was a multi-center study to compare the accuracy of the consumer's self-recognition of recurrent or chronic hives of unknown origin to an assessment by a qualified study physician. This assessment was based on a discussion between the subject and the study physician regarding the subject's medical history, and in some cases, photographs of whealing/rashes. Secondarily, the consumer's ability to understand specific communication points on the label and package insert was studied.
This study involved a single study visit to the research site. No drug was dispensed during the study.
This study included five (5) cohorts:

Cohort 1= CIU sufferers

Cohort 2= General Population

Cohort 3= Low literate

Cohort 4 = “Ask a doctor before use”: Subjects that were either pregnant, nursing/breast-feeding or had liver or kidney disease.

Cohort 5 = “Do not use”: Acute urticaria sufferers

Self-Recognition

Subjects in Cohort 1 (Self-recognized CIU) completed both arms of the study: label comprehension followed by study physician assessment of the subject’s ability to self-recognize CIU.

In order for the subjects to be evaluated on their ability to self-recognize chronic idiopathic urticaria, they underwent a process that allowed them to speak with a nurse and a physician at the research organization’s Central Medical Operations Group (CMOG). There were two physician roles in this study, a CMOG study physician and a coordinating dermatologist. A CMOG study physician spoke with each of the subjects over the telephone. Based on the conversation with the subject, a review of the subject’s medical history, and in some cases, photographs of the subject’s lesions, the study physician assessed whether he/she believed the subject had correctly self-recognized CIU. The coordinating dermatologist reviewed all of the subject data to conclude if the subject accurately self-recognized CIU.

For subjects who did not present with wheals or any obvious symptoms, refused photo consent, or had a photo taken that was of poor photographic quality, the study physician determined accuracy of their self-recognized CIU based on medical history and the subjects’ selection of a photograph that best represented their skin lesions when they experience CIU. Specifically, the subjects were shown two alternative photographs of skin rashes (i.e., chronic urticaria and poison ivy). They were asked to select the letter code of the photograph that looked the most like the rash for which they suffer CIU. Their

response was recorded on the Self-Administered Medical History Form that was sent to the coordinating dermatologist.

Label Comprehension

All subjects completed the label comprehension arm of the study. Subjects in Cohort-1 (*CIU Sufferers*), Cohort 2 (*General Population*), Cohort 3 (*Low Literacy*), and Cohort 5 ("*Do not* u*se"*) completed the full label comprehension questionnaire. Subjects were given scenarios that reflected actual sufferers of CIU and then were asked questions relating to the label and package insert key communication objectives.

Subjects in Cohort 4 (*"Ask a doctor before use")* answered a shortened version of the questionnaire. The main purpose of this interview was to determine if consumers who were pregnant/nursing or had a liver or kidney disease understood that they need to ask a doctor before using Claritin® when asked to assume they had been diagnosed by a doctor as having CIU. All subjects were told to refer back to the label and package insert as often as needed.

STUDY POPULATION

Source and Number of Subjects

A total of 565 subjects were interviewed for this study. The population consisted of adult males and females, 18 years of age and older. An enriched population of adults 18 years of age and older were included for Cohorts 1, 3, 4, and 5.

Chronic Idiopathic Urticaria (CIU) Sufferers (n=196)

This population was pre-recruited through advertising and direct mail and then screened for participation. As part of the screening procedure, subjects were asked to bring with them the name and telephone number of the physician who diagnosed their CIU and to sign a limited release of medical information form. This consent permitted contact of their physician, if necessary.

General Population (n=116)

This population was recruited via mall intercept in a broad U.S. market distribution to ensure a wide range of socio-economic and educational levels.

Low Literate (n=96)

All subjects were required to take the REALM (Rapid Estimate of Adult Literacy in Medicine) test to determine reading literacy. Low literate is defined as a subject who reads at a maximum grade equivalent of seventh-eighth grade or below as measured by the REALM literacy-screening instrument.

Subjects in other cohorts who were low literate also counted towards this cohort. The remaining consumers for this cohort were recruited and interviewed at off-site locations known to have a higher concentration of low literate adults, such as neighborhood grocery stores, convenience stores and apartment complexes.

"Ask a doctor before use" (liver or kidney disease/pregnant or nursing) (n=114)

This cohort included subjects who were pregnant, nursing, or had liver or kidney disease. Subjects who were pregnant/nursing were recruited via mall intercept. Those subjects who had liver or kidney disease were pre-recruited at special sites and by using agency databases, and asked to come to a central location for the label interview.

"Do not use" (Acute hive sufferers) (n=102)

This cohort included subjects who had self-reported acute urticaria. These subjects were recruited via mall intercept.

STUDY DATES

Interviewing for this study began on November 14, 2001 and ended on December 12, 2001.

SUBJECT DISPOSITION

A total of 565 subjects were interviewed for this study, distributed among the cohorts as shown below.

Final Sample Size Within Cohorts

	Total	CIU Sufferers	General Population	Low Literate Population	"Ask a Dr. first" Preg/Nsg./ Liver/ Kidney	"Do not use" Acute Hive Sufferers
Completed Interviews	565	196	116	96	114	102

The number of interviews conducted in each cohort does not add to the "total" as subjects could count toward more than one cohort.

STUDY LOCATIONS

Twenty-four (24) marketing research facilities located in twenty-one (21) geographically dispersed markets across the United States were used to complete recruiting and enrollment for this study.

Because of the need to pre-recruit Cohort 1 - CIU Sufferers, these same sites also conducted telephone interviews to screen subjects who responded to a newspaper or radio advertisement. If, based on the screening questionnaire, the subjects qualified for Cohort 1, they were scheduled for an appointment at the research site to undergo the interview process.

Three (3) off-site locations conducted interviewing for Cohort 3 - Low Literate. Low literate recruiting was conducted in facilities such as convenience stores, grocery stores, apartment complexes, and other locations that provide a higher concentration of low literate adults.

Three (3) other off-site locations conducted the interviewing for Cohort 4 – "Ask a doctor before use" (liver/kidney disease subjects only). Those subjects who had liver or kidney disease were pre-recruited at these sites as well as by agency databases, and asked to come to a central location for the label interview.

DATA MANAGEMENT

The completed questionnaires were shipped from the sites to the research organization for data entry. All data was entered using the double data entry verification process. All verbatim responses were reviewed and classified into appropriate codes. Tabulations were developed and used for analysis.

SUMMARY OF FINDINGS

Self-Recognition

Subjects demonstrated the ability to self-recognize CIU. Nearly all (94%) of the subjects were confirmed by the physician as having CIU.

Label Comprehension – Package Label

Product use

When asked on an open-ended basis what the product was used for, CIU sufferers demonstrated the strongest understanding (77% correct/acceptable) of the 5 cohorts. The other cohorts scored below this level (range of 49% to 58% correct/acceptable). The most common incorrect answer (mentioned by 20% of subjects) was "hives/itching due to hives." However, it is worth noting that it is extremely difficult to elicit a very specific answer (i.e. chronic hives/hives of an unknown source) from subjects in an open-ended question such as this.

When presented with a list of correct and incorrect product use conditions and asked to select the conditions for which the product is intended to be used, CIU sufferers demonstrated the strongest understanding (71% correct/acceptable) of the 5 cohorts. The other cohorts scored below this level (range of 38% to 49% correct/acceptable). Overall, most of the subjects (92%) stated this product is intended for recurring or chronic hives of an unknown cause, but were not considered "correct/acceptable" because they also stated it is indicated for other incorrect conditions.

Nearly one- quarter (22%) stated this product is intended for hay fever. However, subjects demonstrated a stronger understanding of the uses of Claritin® (66% - 99% correct/acceptable range across scenarios and cohorts) when presented with correct and incorrect usage scenarios.

Self-Selection

"Okay to use" (CIU Sufferers)

All of the CIU sufferers (100%) for whom drug use was appropriate (i.e., who were "okay to use the product") correctly self-selected the product for their use or stated they would ask their doctor prior to use.

"Ask a doctor first" and "Do not use" (liver/kidney disease and pregnant/nursing, acute hive sufferers, not experience hives)

The majority (80%) of the subjects who should "ask a doctor before using" this product understood this warning and either correctly stated they would ask a doctor before using it or they did not select the product as one they could use.

Almost three-fourths (70%) of the general population and more than two-thirds (65%) of the low literate population who were not appropriate candidates for Claritin® understood this and either correctly de-selected the product or stated they would "ask a doctor" prior to use.

More than half (54%) of the subjects who suffer from acute hives and should "not use the product" either correctly de-selected the product or stated they would "ask their doctor" prior to use. Comprehension scores among this population improved (75%) for a direct scenario regarding use of the product for acute hives.

Warnings

Consumers across all cohorts demonstrated a strong understanding (75% - 100%) of all the warnings. Notably, CIU sufferers demonstrated a strong understanding that this product should not be used in situations in which serious symptoms (e.g., trouble swallowing, wheezing or problems breathing, etc.) are present (91% and 96% correct/acceptable for the two scenarios that addressed this objective).

Directions

Overall, subjects demonstrated a strong understanding (67% - 100%) of all the directions for use. Regarding the direction of not taking more than one tablet in a 24 hour period, the low literate population's understanding of this was somewhat less (78%) than the other cohorts.

Label Comprehension – Package Insert

Subjects demonstrated strong understanding (84% - 99%) that Claritin® is not indicated for acute hives. Most subjects (90% - 96%) understood when to stop taking Claritin® after the itching stops. Comprehension was lower (57% - 81%) regarding the implications of taking more than one tablet within 24 hours, especially among the low literate (57%).

CONCLUSIONS

Self-Recognition

CIU sufferers can accurately self-recognize (94%) the condition and symptoms of CIU upon recurrence.

Label Comprehension

Overall, consumers understood the uses of Claritin®, the label warnings, and directions with the exception of those findings noted below.

When presented with correct and incorrect product use situations in scenarios, non CIU sufferers demonstrated a strong understanding (66% - 97%). However, this

level decreased (38% - 58%) when subjects were asked about the uses of the product on an open-ended basis. The most common incorrect answer given by acute hives sufferers (mentioned by 22% of subjects) was “hives/itching due to hives.” While the conservative approach was taken in categorizing this response as an “incorrect” response, in fact it is not incorrect since it includes hives of an unknown source.

When presented with a scenario of acute hives, three-fourths (75%) of acute hive sufferers understood Claritin® is not indicated for this condition. When acute hive sufferers were asked whether Claritin® is intended for their use, more than half (54%) either correctly de-selected the product or indicated they would ask their doctor prior to use.